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TITLE: 6TH INTERNATIONAL CONFERENCE ON HYPERTONIC RESUSCITATION (SALT 6) - JUNE 2-3, 1994

PRINCIPAL INVESTIGATOR: Robert Gunther, Ph.D.

CONTRACTING ORGANIZATION: University of California, Davis
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October 1, 1994 Final Proceedings

6th International Conference on Hypertonic Resuscitation (Salt 6) - June 2-3, 1994

Grant No.
DAMD17-94-J-4012

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The International Conference on Hypertonic Resuscitation (Salt 6) was held in Teton Village, Wyoming on June 2-3, 1994. Report includes the program and abstracts. The conference was a very successful meeting and many considered it the most successful and informative in the series.

Conference, Hypertonic, Resuscitation, RAD II

GENERAL INSTRUCTIONS FOR COMPLETING

International Conference on Hypertonic Resuscitation

PROGRAM

WEDNESDAY, June 1, 1994

4:00-5:45pm	**REGISTRATION** **Rendezvous Room and Deck**
6:00pm	**WELCOME WINE AND CHEESE** **Rendezvous Room and Deck**

THURSDAY, June 2, 1994

7:00 - 8:15 am	**REGISTRATION AND CONTINENTAL BREAKFAST** **Rendezvous Room**
8:15 - 8:30 am	**Welcome Introduction** Robert Gunther and Michael Krausz

SLIDE SESSION I: Thermal Injury and Hypertonic Saline
Session Chairs: Henning Onarheim and Jureta Horton

8:30 - 8:45 Abstract #3	**Brian Button**, Univ. of Texas Medical Branch, Galveston *Initial Fluid Requirements and Hemodynamic Effects Using Lactated Ringer's Hetastarch and Hypertonic Saline Dextran Following 85% TBSA Partial Thickness Scald Injury*
8:45 - 9:00 Abstract #12	**Jureta W. Horton**, Univ. of Texas Southwestern Med. Center, Dallas *Hypertonic Saline Dextran Administration Can Be Delayed After Crystalloid Resuscitation from Burn Injury*
9:00 - 9:15 Abstract #17	**Michael P. Kinsky**, Shriners Burns Inst. & U. of Texas Med. Branch *Initial Resuscitation of Burn Injury with Hypertonic Saline Dextran (HSD) Prevents the Reversal of the Plasma-Interstitial Oncotic Gradient in Non-Burned Skin*
9:15 - 9:30 Abstract #20	**Anne E. Missavage**, Regional Burn Center, Univ. of Calif., Davis *Early, Low-Volume Hypertonic Saline-Dextran Resuscitation for Thermal Injury*
9:30 - 9:40	**COFFEE BREAK**

SYMPOSIUM I: Dehydration & Hypertonic Resuscitation
Session Chair: Michael Dubick

9:40 - 9:45	**Introduction:** Michael Dubick
9:45 - 10:05	**Charles E. Wade**, NASA-AMES *Dehydration: Subsequent Impact on Traumatic Hemorrhage*
10:05 - 10:25	**Jill L. Sondeen**, U.S. Army Institute of Surgical Research *Dehydration State and Hypertonic Saline/Dextran Resuscitation of Hemorrhagic Shock*

10:25 - 10:45 **M. Dan McKirnan**, Univ. of Calif., San Diego
HSD vs LR Resuscitation of Hemorrhagic Shock in Dehydrated Pigs

10:45 - 11:05 **Candace Matthew**, USARIEM
Administration of HSD in the Presence of Hyperthermia and Dehydration: Studies in Rats and Swine

11:05 - 11:25 **Michael Krausz**, Carmel Hospital, Haifa, Israel
Use of Hypertonic Saline in an Uncontrolled Hemorrhage Rat Model: Effects of Dehydration

11:25 - 12:00 **Panel Discussion**

12:00 - 1:30 **LUNCH / Hamburger Cookout**
Dining Room Deck

SLIDE SESSION II: Hemorrhage & Resuscitation 1: Physiological Mechanisms
Session Chair: Nguyen Kien

1:30 - 1:45
Abstract #8 **Lorenz Frey**, University of Munich, Germany
Is Sodium-Acetate-Dextran Superior to Sodium-Chloride-Dextran for Resuscitation from Traumatic/Hemorrhagic Shock?

1:45 - 2:00
Abstract #13 **J. Jonas**, Johannes Gutenberg Univ. Mainz Klinikum
The Effect of 7.5% NaCl/10% Hydroxyethyl Starch on the Intestine after Superior Mesenteric Artery Occlusion

2:00 - 2:15
Abstract #14 **Wolfgang Junger**, Univ. of Calif., San Diego Med. Center
Hypertonic Saline Enhances Cellular Immune Function

2:15 - 2:30
Abstract #32 **Lisbeth Waagstein**, University of Göteborg, Sweden
Hypertonic Saline in the Treatment of Acute Limb Ischemia

POSTER SESSION I: Hemorrhage & Resuscitation 2

2:30 - 4:00 **Viewing**

3:00 - 3:15 **REFRESHMENTS**

4:00 - 5:00 **Poster Discussion I**
Session Chairs: Mauricio Rocha e Silva and Michael Krausz

4:05 - 4:10
Abstract #2 **Renato C. Baena**, Univ. of Sao Paulo, Brazil
New Evidence for the Participation of Neural Hemodynamic Reflexes Evoked by Hypertonic Resuscitation in Hemorrhagic Shock in Dogs

4:10 - 4:15
Abstract #4 **Valerie Coppes**, U.S. Army Institute of Surgical Research
Hemodynamic, Plasma, and Urinary Responses to Different NaCl Solutions with Dextran-70 in Hemorrhaged Sheep

4:15 - 4:20
Abstract #22 **Hiromaru Ogata**, Dokkyo Univ. School of Medicine, Mibu, Japan
Hypertonic Saline Improves Cerebral Oxidative Metabolism and Cytochrome AA3 Redox State During Hemorrhagic Hypotension in Dogs

4:20 - 4:25
Abstract #25

Zehava Ovadia, Tel Aviv Univ. Sheba Med. Center, Israel
The Effect of Blood and Saline Transfusion Following Hemorrhage on Non-Invasive Measurements of Microcirculatory Hemodynamics

4:25 - 4:30
Abstract #31

Jill L. Sondeen, U.S. Army Inst. of Surgical Research
Comparison of 7.5% NaCl 6% Dextran-70 Resuscitation of Hemorrhage Between Euhydrated and Dehydrated Sheep

4:30 - 4:35
Abstract #6

Geir Ivar Elgjo, National Inst. of Occupational Health
Treatment of Uncontrolled Hemorrhage with Hypertonic Saline (NaCl 8.0%): Differential Effects of Injury and of Treatment on Selective Abdomnal Arterial vs. Venous Injury

4:35 - 4:40
Abstract #18

Michael Krausz, Carmel Hospital, Haifa, Israel
Hypertonic Sodium Acetate Treatment of Uncontrolled Hemorrhagic Shock (UCHS) in Awake Rats

4:40 - 4:45
Abstract #19

Tetsuya Matsuoka, Univ. of California, Davis
Hypertonic Saline Resuscitation of Uncontrolled Abdominal Visceral Hemorrhage

4:45 - 4:50
Abstract #26

Luiz F. Poli de Figueiredo, Univ. of Sao Paulo, Brazil
Hemodynamic Effects of Small Volume Hypertonic Solutions in Lower Torso Ischemia and Reperfusion in Hemorrhagic Shock

4:50 - 4:55
Abstract #34

William C. Watson, Univ. of Texas Medical Branch
Resuscitation of Uncontrolled Hemorrhagic Shock Using Hypertonic Solutions and Lactated Ringer's

FRIDAY, June 3, 1994

7:00 - 8:15

REGISTRATION AND BUFFET BREAKFAST
Rendezvous Room

8:15 - 8:30

Announcements: Robert Gunther & Michael Krausz

SLIDE SESSION III: Hypertonic Resuscitation: Heart & Brain
Session Chair: David Wisner

8:30 - 8:45
Abstract #10

Roger Härtl, Dept. of Neurosurgery, Cornell Univ. Med. College
The Effect of Hypertonic Saline/Dextran on Cerebral Edema after Experimental Brain Injury and Hemorrhagic Shock

8:45 - 9:00
Abstract #15

Józef Kaszaki, Szent-Byorgyi Albert Medical Univ., Hungary
Role of Histamine Receptors and Endothelium in Cardiac Contractility Changes Following Hypertonic Saline Infusion

9:00 - 9:15
Abstract #30

Azad Sheikh, Univ. of Calif., Davis Medical Center
Effect of Hypertonic Fluids on ICP & Brain Water Content in Combined Head Injury and Hemorrhagic Shock

9:15 - 9:30
Abstract #35

M. Welte, University of Munich, Germany
Effects of NaCl 7.2%/10% Dextran-60 on Global and Local Myocardial Performance During Resuscitation from Hemorrhagic Shock

9:30 - 9:45 **COFFEE BREAK**

SYMPOSIUM II: Hypertonic Saline & Intraoperative Volume Support
Session Chair: George Kramer

9:50 - 10:10

Jocaim Boldt, Abtielung for Anesthesiology, Germany
Hypertonic Saline-Hetastarch for Cardiac Surgery

10:10 - 10:30

Riad N. Younes, University of Sao Paulo, Brazil
Intraoperative Use of Hypertonic Saline During Aortic Clamping-Declamping

10:30 - 10:50
Abstract #28

Mark A. Rudin, Kantonsspital Winterthur, Switzerland
Changes in Cerebrospinal Fluid Osmolaltiy After Intraoperative Volume Replacement with Hypertonic-Hyperoncotic Saline/Dextran vs. Ringer's Lactate/Gelatine

10:50 - 11:10
Abstract #37

Steven R. Hayes, Univ. of Kentucky, Chandler Medical Center
Hypertonic Saline Administration Decreases Facial Swelling, Time to Discharge and ICU Days in Oral Surgery Osteotomy Patients

11:10 - 11:30 **Panel Discussion**

POSTER SESSION II: Hemorrhage & Resuscitation 3

11:30 - 12:15 **Viewing**

12:15 - 1:30 **LUNCH / Sandwich Buffet**
Dining Room Decks

1:30 - 2:10 **Poster Discussion II**
Session Chairs: Charles Wade & Robert Gunther

1:35 - 1:40
Abstract #1

Mayuki Aibiki, Medical University of South Carolina
Role of Autonomic Nervous System in Acute Pressor Effects Induced by 3.5% Hypertonic Chloride Solution in Hemorrhaged Rabbits

1:40 - 1:45
Abstract #5

Michael A. Dubick, U.S. Army Inst. of Surgical Research
Hematological Analysis of Blood from Hemorrhaged Rabbits and Pigs Infused with 7.5% NaCl/6% Dextran-70 (HSD)

1:45 - 1:50
Abstract #9

Robert Gunther, University of California, Davis
Role of Glucose and Amino Acids in 2400 mosm Isosal: Osmotic Shift of Sodium Free Water

1:50 - 1:55
Abstract #16
Józef Kaszaki, Szent-Byorgyi Albert Medical Univ., Hungary
In Vitro Study of Endothelium Dependent Histamine Release from Canine Mesenteric Arterial Segments

1:55 - 2:00
Abstract #21
Lena K. Nutt, University of Texas Medical Branch
Hypertonic Saline/Dextran Prime for Cardiopulmonary Bypass Reduces Overall Fluid Balance and Gut Tissue Water

2:00 - 2:05
Abstract #23
Hiromaru Ogata, Dokkyo Univ. School of Medicine, Mibu, Japan
Inhibitory Effect of Hypertonic Saline on the Delayed Neuronal Death in Hippocampus CA1 Area of the Gerbils Subjected to Transient Global Ischemia

2:05 - 2:10
Abstract #24
Henning Onarheim, Haukeland Univ. Hospital, Norway
Fluid Shifts Following Administration of 7% Sodium Chloride

2:10 - 2:30 **REFRESHMENTS**

SLIDE SESSION IV: Clinical Trials
Session Chair: James Holcroft

2:30 - 2:45
Abstract #7
Marcus Fähnle, University of Heidelberg, Mannheim, Germany
Comparison of Titrated Dosage of Hypertonic-Hyperoncotic and Isotonic-Hyperoncotic Solutions in Cardiac Risk Patients

2:45 - 3:00
Abstract #11
James Holcroft, Univ. of California, Davis
Meta-Analysis of Survival for Prehospital Resuscitation of Hypotensive Patients with Hypertonic/Hyperoncotic Solutions

3:00 - 3:15
Abstract #27
Mauricio Rocha e Silva, University of Sao Paulo, Brazil
Hypertonic-Hyperoncotic Saline Solution for the Treatment of Post-Traumatic Hypotension in the Emergency Room. The Brazilian Multicenter Trial

3:15 - 3:30
Abstract #29
Michael Schroth, University of Heidelberg, Mannheim, Germany
The Influence of Hypertonic-Hyperoncotic Infusion on the Excretion of Atrial Natriuretic Factor (ANF) in Normovolemia

3:30 - 3:45
Abstract #33
Charles E. Wade, Univ. of Texas Medical Branch, Galveston
Efficacy of Hypertonic Saline/Dextran (HSD) or Hypertonic Saline (HS) on Survival Following Traumatic Injury: A Meta-Analysis

3:45 - 4:00
Abstract #36
Riad N. Younes, University of Sao Paulo, Brazil
Prognosis Following the Administration of Hypertonic/Hyperoncotic Solutions in Hypovolemic Patients

4:00 - 4:30 **Concluding Panel Discussion: Summation & Announcements**

6pm **NO HOST BAR**
BBQ Area

7pm **BANQUET / WESTERN COOKOUT**

SALT 6

Teton Village, Wyoming

June 2–3, 1994

International Conference on Hypertonic Resuscitation

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ROLE OF AUTONOMIC NERVOUS SYSTEM IN ACUTE PRESSOR EFFECTS INDUCED BY 3.5 % HYPERTONIC CHLORIDE SOLUTION IN HEMORRHAGED RABBITS

M. Aibiki, K. Seki, S. Ogura, Y. Shirakawa and K. Ogli.

Kagawa Medical School, Department of Anesthesiology and Emergency Med. 1750-1, Ikenobe, Miki, Kita, Kagawa, 761-07, Japan
(Present Address: Department of Physiology of MUSC, 171 Ashley Ave. Charleston, SC, 29425)

Background and Methods: Neural reflex mechanism for the pressor effects with hypertonic sodium chloride solution (HTS) is still controversial. We therefore designed this study to evaluate the changes in hemodynamics and renal sympathetic nerve activity using a direct measurement when 3.5 % HTS at half volume of shed blood was administered to fifteen hemorrhaged rabbits that were anesthetized with urethane. The animals were divided into the following three groups: intact group, animals with intact neuraxis (N=5); vagotomy group, cervical vagotomized animals with intact carotid sinus and aortic nerves (N=5); SAD group, the carotid sinus and aortic nerves denervated animals with intact vagal nerves (N=5). After hemorrhagic hypotension of 40 mmHg for ten minutes, HTS was infused for an approximate 1 min period. ANOVA followed by a Scheffe's F-test was used for statistical analysis of the data ($p<0.05$).
Results: In the intact animals receiving HTS, a sympathetic activation (155 ± 20 % of the pre-injection level) developed and this was associated with a rapid increase in systemic blood pressure. This sympathetic increase was followed by a return to the pre-injection level in response to an increase in central venous pressure. However, in the vagotomized animals, HTS resuscitation produced a sustained sympathetic augmentation associated with pressor effects. In contrast, in the SAD group administered HTS, neither a sympathetic enhancement nor acute increases in systemic blood pressure as observed in the other groups occurred.
Conclusion: These results suggest that 3.5 % HTS may produce a sympathetic activation leading to acute pressor effects, which may be mediated through the sino-aortic nerves but not through the vagal nerves.

NEW EVIDENCE FOR THE PARTICIPATION OF NEURAL HEMODYNAMIC REFLEXES EVOKED BY HYPERTONIC RESUSCITATION IN HEMORRHAGIC SHOCK IN DOGS.

Renato C. Baena, Irineu T. Velasco and Mauricio Rocha e Silva.

Heart Institute, Faculdade de Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.

Background: We previously demonstrated that the first passage of hypertonic blood through the cardiopulmonary area was responsible for eliciting early hemodynamic and respiratory responses. These consisted of byphasic decreases in heart rate and blood pressure accompanied by byphasic periods of tachypnea. The first component of this response was recognized as the pulmonary chemoreflex, but the second one remains partially obscure. The purpose of the present study was to determine potential beneficial effects induced by these responses during the hypertonic resuscitation.

Methods: Eighteen pentobarbital anesthetized dogs prepared for hemodynamic measurements and blood oxymetry were randomly assorted into three groups and subjected to a pressure driven hemorrhage protocol described elsewhere (Prist et al in Circ. Shock 36: 13-20, 1992). After 30 minutes of hemorrhage, bleeding was interrupted for a period of 3 minutes and dogs pertaining to two out of the three groups received a hypertonic solution (NaCl 7.5%) infusion through a pump adjusted to deliver 50 ml in 78 seconds. These two groups differed by the site of infusion: femoral vein for the group **HSV** and descending aorta (at the level of the diaphragm) for group **HSA**. The third group, **CTL**, received no infusion. Pressure driven hemorrhage was continued throughout the postresuscitation period.

Results: There were no statistical differences among groups for any of the measured parameters, up to the time of infusion. **CTL** dogs bled 50.1±4.24 ml/kg and survived to 76.7 ±15.4 min postzero; **HSV** dogs bled 60.2±3.59 ml/kg and survived to 104.5±21.8 min postzero with prolonged periods of recovery of vascular resistance, cardiac output, oxygen availability (DO_2) and oxygen uptake (VO_2); **HSA** dogs bled 56.5±6.24 ml/kg and survived to 87.5±10.5 min postzero with transient recovery periods of blood pressure and cardiac output but no other signs of improvement.

Conclusion: In spite of the same volume expansion promoted by the 2 varieties of hypertonic resuscitation, the **HSV** group exhibited improved hemodynamic and oxymetric conditions when compared with the **HSA** group. The difference may have been caused by the decreased vascular resistance, observed only in the **HSV** group. Finally, we may speculate that the first passage effect of the hyperosmolarity through the cardiopulmonary area would be ultimately responsible for these observations, since it does elicit important vasodilator neural reflexes.

Research supported by FAPESP and Fundação E. J. Zerbini

INITIAL FLUID REQUIREMENTS AND HEMODYNAMIC EFFECTS USING LACTATED RINGER'S, HETASTARCH AND HYPERTONIC SALINE DEXTRAN FOLLOWING 85% TBSA PARTIAL THICKNESS SCALD INJURY.

Brian Button, Michael P Kinsky, Somes C Guha, Daniel L Traber and George C Kramer

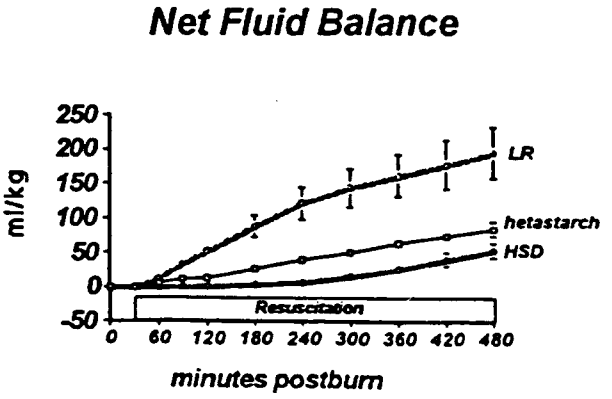
Departments of Anesthesiology and Surgery, The University of Texas Medical Branch and Shriners Burns Institute, Galveston, Texas 77555

Background: Colloid solutions can reduce volume requirements of hemorrhagic shock Colloids, however, are usually not used in early burn resuscitation, since it has been hypothizsed that increased capillary permeability make them no more effective than isotonic crystalloids. We compared the early use of colloid (6% Hetastarch) and hyperosmolar crystalloid/colloid (7.5% NaCl-6%-Dextran [HSD]), followed by lactated Ringer's (LR) supplement in each group, versus using only LR.

Methods: Female sheep (35-45 kg) were chronically instrumented with Doppler flow probes, Swan-Ganz thermodilution catheters, and femoral artery catheters. Experiments were performed 7 days postsurgery. Sheep were anesthetized with isoflurane and ventilated to normocapnia. Baseline parameters were recorded, samples obtained, and the animals were subjected to a partial thickness 85% TBSA scald injury with one application of 85°C water. Resuscitation was initiated 30 minutes after injury with a blinded test solution (10 ml/kg) of either LR, Hetastarch, or HSD. After the infusion of the test solution, resuscitation was continued with LR for the remainder of the experiment. Infusion of all solutions were titrated to achieve and maintain baseline oxygen delivery. Sheep were euthanized 8 hours postinjury.

Results: Oxygen delivery was restored to baseline in all animals throughout the postinjury resuscitation. Urine output, superior mesenteric artery and renal blood flow were restored to near-normal levels with no significant difference between groups. Pulmonary wedge and central venous pressures were similarly elevated in all groups before and during resuscitation despite restoration of baseline cardiac outputs, suggesting some level of cardiac failure. The net fluid requirements of resuscitation for the three groups are shown. The fluid requirements were significantly less in the HSD- and Hetastarch-treated group than in the LR group.

Conclusion: HSD dramatically reduced fluid volume requirements during the first 4 hours of resuscitation, while subsequent LR requirements were paralleled in all groups. Both HSD and Hetastarch significantly reduced isotonic fluid requirements by 65% and 50%, respectively, for the first 8 hours of resuscitation without any compromise of systemic perfusion or oxygen delivery. Experiments of longer duration are needed to determine if volume sparing effects can be sustained, and to determine the clinical benefits of such therapies.



HEMODYNAMIC, PLASMA, AND URINARY RESPONSES TO DIFFERENT NaCl SOLUTIONS WITH DEXTRAN-70 IN HEMORRHAGED SHEEP

Valerie G Coppes, Jill L Sondeen, Robert A Gunther, and Michael A Dubick

U S Army Institute of Surgical Research, Fort Sam Houston TX 78234 and Department of Surgery, University of California, Davis CA 95616

Background: 7.5% NaCl-6% Dextran-70 (HSD) has been shown to be an effective, small volume resuscitation fluid following hemorrhage. We compared 4 different sodium concentrations and 12% Dextran-70 (D70) to HSD in our continuing search for the most effective small-volume resuscitative fluid.

Methods: We used chronically-instrumented, euhydrated, adult ewes to study the hemodynamic, plasma (P), and urinary excretion (E) responses to 4 different test solutions (0.9, 3.75, 7.5 and 10% NaCl in 12% D70) compared to HSD. All sheep were bled to 50 mmHg mean arterial pressure (MAP). After 2 h of hypotension, they received a 4 ml/kg bolus of a test solution and data were collected over 90 min.

Results: Hemodynamic responses to all solns were similar for MAP, heart rate, and central venous pressure. All solns restored cardiac output (CO) to baseline levels after 15 min, regardless of D70 concentration. However, the solns with 7.5 and 10% NaCl resulted in early significant differences in CO (CO @ 5 min: 0.9% = 3.8 ± 0.1; 3.75% = 4.6 ± 0.4; 7.5% & 10% = 6.9 ± 0.2 L/min) and total peripheral resistance (TPR @ 5 min: 0.9% = 26 ± 1; 3.75% = 22 ± 2; 7.5% & 10% = 15 ± 1 PRU), although these values converged after 10 min. P_{Na} was significantly higher in the 7.5 and 10% NaCl soln groups (162 ± 1) than in the 0.9% soln group (149 ± 2 mEq/L), and P_{D70} was greater in the 12% D70 soln groups (802 ± 51) versus HSD group (377 ± 39 mg/dl). P_K, $P_{protein}$, and $P_{creatinine}$ were similar among groups. There was a %NaCl-dose-related increase in urine flow rate with (10% & 7.5% = 1.6 ± 0.2) > (3.75% = 0.7 ± 0.4) > (0.9% = 0.4 ± 0.2 ml/min). E_{Na} with the 10% soln (313 ± 156) was greater than with the 0.9% (3.2 ± 1.6) or 3.75% (26 ± 13) solns, but was not significantly different from 7.5% solns (138 ± 69 µEq/min). There was no difference in the E_K or $E_{creatinine}$ among the groups. Despite the doubling of P_{D70} between the HSD and 12% D70 soln groups, there were no dose-related differences in E_{D70} (HSD = 17.5 ± 9; 7.5% / 12% = 19.9 ± 10 mg/min).

Conclusion: Since both 7.5 & 10% NaCl solns were equally effective in improving initial CO compared to 0.9 and 3.75% soln, there seems to be no advantage in going to the 10% soln with respect to the improvement in hemodynamics. However, it is clearly the D70 moiety which causes sustained, improved CO. Although earlier studies suggested that 7.5%/12% D70 may be superior to HSD, the present study showed no significant difference. The finding that E_{D70} excretion was independent of P_{D70} concentration was unexpected. The mechanism of this independence is unknown; there were no differences in GFR. We previously showed that there was no apparent plasma binding of D70, & others have shown there is no renal tubular reabsorption or secretion of D70. There may be a maximal rate of filtration of D70, perhaps due to some kind of interaction of D70 with the glomerular membrane.

COMPARISON OF TITRATED DOSAGE OF HYPERTONIC-HYPERONCOTIC AND ISOTONIC-HYPERONCOTIC SOLUTIONS IN CARDIAC RISK PATIENTS

Marcus Fahnle, Michael Schroth, Klaus Ellinger, Michael D. Albrecht

Institute of Anesthesiology, Klinikum Mannheim University of Heidelberg, 68167 Mannheim Germany

Background: Hypertonic-iso/hyperoncotic solutions have been subject of intensive experimental and clinical research since several years. In nearly all studies a fixed dosage of 4 ml/kg body weight has been used. Yet no study exists to prove wheather this is the optimal dosage especially in cardiac risk patients. Using a fixed 4 ml dosage preclinically in poorly monitored cardiac risk patients could be dangerous. To find the optimal dosage we titrated a hypertonic-hyperoncotic solution individually in well monitored cardiac risk patients with slight hypovolemia before aneurysmectomy at the infrarenal abdominal aorta.

Methods: We compared preoperative volume-loading according to the individual Frank-Starling relation with either 10% hydroxyethylstarch/ 7.5% NaCl (HHT-HES) or 10% hydroxyethylstarch/ 0.9% NaCl (HES) in a randomized, controlled, double blind clinical study (with permission of the ethical committee). Under invasive hemodynamic monitoring (arterial catheter, pulmonary artery catheter and ECG with limb and precordial leads) we started with stepwise infusion of either HHT-HES or HES in 50 ml steps. The endpoint of stepwise infusion represented the highest cardiac index (CI) at the lowest possible wedge pressure (PCWP) (= the turning point of the individual Frank Starling relation = "best wedge condition"). All hemodynamic parameters, continous ST-registration, fluid balance and respiratory parameters were continuously recorded during and after volume-loading as well as intra- and postoperatively.

Results: In both groups we achieved the individual "best wedge condition" at the same filling pressure level. To reach the individual "best wedge" 167.5 ml (±45,5 ml/ = 2.41 ml/kg bw) of HHT-HES and 440 ml (26,15 ml/ = 5.98 ml/kg bw) of HES were necessary. The CI increased from 2.72 l/min/m^2 (±0.53) to 4.35 l/min/m^2 (±1.04/ = +59.92%) in the HHT-HES group and from 2.9 l/min/m^2 (±0.75) to 3.79 l/min/m^2 (±1.17/ = +30.68%) in the HES group. Both increases were significant ($p<0.001$) with a significant higher increase in the HHT-HES group ($p<0.001$). No ST-segment deviation, no increase of calculated oxygen consumption, no hypotension did occur in both groups. Significant increases of PCWP, pulmonary artery pressure (PAP), central venous pressure (CVP) and left/ right ventricular stroke working index (LVSWI/RVSWI) ($p<0.01$) occured without any significant differences between the groups ($p<0.05$). In the HHT-HES group we found a significant increase of systolic arterial pressure ($p<0,05$) during volume loading.

1) Volume demand was 2.5 higher in the HES group. 2) Optimum dosage of HHT-HES was 2.41 ml/kg bw. 3) CI in the HHT-HES group was significant higher. 4) No negative side effects especially no hypotension occured in the HHT-HES group [1,2,3].

Conclusions: ❶ Commonly used 4 ml/kg bw dosage of HHT-HES is to high in cardiac risk patients and slight hypovolemia. ❷ HHT-HES shoud be given in an individual titration and not in a fixed dosage. ❸ HHT-HES in our investigation had a positive inotropic effect. ❹ With the individual titration no dangerous hypotension occured.

References: 1. Anesth-Analg 73: 597-602 2. Zentralbl-Chir 118: 257-66 3. Zentralbl-Chir 118: 250-6

IS SODIUM-ACETATE-DEXTRAN SUPERIOR TO SODIUM-CHLORIDE-DEXTRAN FOR RESUSCITATION FROM TRAUMATIC/HEMORRHAGIC SHOCK?

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Background: Small volumes (4 ml/kg b.w.) of hypertonic sodium chloride dextran have been shown to effectively restore cardiac output and nutritional blood flow and to increase arterial pressure in severe hemorrhagic shock. It has been suggested to replace the chloride anion with acetate providing a solution without the risk of hyperchloremia and the advantage of supplying buffering base to optimize hypertonic resuscitation.

Methods: This study compares the effects of hypertonic sodium chloride dextran solution (7.2% NaCl/10% dextran 60: NaCl-Dx; n=7) with sodium acetate dextran (10.4% Na-Acetate/10% dextran 60: NaAc-Dx; n=6) on hemodynamic, oxygen transport and metabolic parameters. Both solutions had the identical osmolality (2,400 mOsmol/kg). Dogs (16.9 ± 1.9 kg) were anesthetized and mechanically ventilated. Shock was induced by exteriorization of intestine and blood withdrawal (50% of blood volume) to maintain mean arterial blood pressure (MAP) at 40 mmHg for 75 minutes. Thereafter resuscitation was performed either with NaCl-Dx (4 ml/kg over 2 min.) or NaAc-Dx (4 ml/kg over 4 minutes).

Results: During hypertonic resuscitation, there was a short lasting decrease in MAP, which was more pronounced in the NaAc-Dx group (ΔMAP -7.3±2.5 mmHg). Cardiac Index and oxygen consumption were normalized within 5 minutes after resuscitation with both solutions. In NaAc-Dx treated animals MAP remained at lower values as compared to NaCl-Dx treated dogs at 5 and 30 min after resuscitation (52±3 vs. 74±6, and 61±7 vs. 79±12 mmHg; $p<0.05$). Arterial pH (7.27±0.02 vs. 7.17±0.06 at 5min, 7.31±0.04 vs. 7.23±0.07 at 30 min and 7.32±0.05 vs. 7.26±0.05 at 60 min, $p<0.05$) and bicarbonate concentrations (24.4±2.1 vs. 16.7±9.5 at 5 min, 26.6±1.8 vs. 18.0±1.9 at 30 min and 27.5±2.1 vs. 19.1±1.7 mmol/l at 60 min, $p<0.05$) in the plasma were normalized shortly after NaAc-Dx infusion, however, hyperlactemia persisted after resuscitation with NaAc-Dx (7.10±1.48 vs. 3.82±1.45 at 30 min, and 5.40±1.73 vs. 2.71±0.89 mmol/l at 60 min, $p<0.05$).

Conclusion: We conclude from these results that NaAc-Dx offers no definitive advantages as compared to NaCl-Dx for resuscitation from traumatic-hemorrhagic shock in our model of controlled hemorrhage. Because arterial hypotension during resuscitation may compromise myocardial perfusion. Although NaAc-Dx instantaneously improved acid base status, hyperlactacidemia persisted.

HEMATOLOGICAL ANALYSIS OF BLOOD FROM HEMORRHAGED RABBITS AND PIGS INFUSED WITH 7.5% NACL/6% DEXTRAN-70 (HSD).

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Background: With expanded research interest in the development of hypertonic saline/dextran solutions for the treatment of hemorrhagic hypotension, concerns have arisen regarding adverse effects on hemostasis. In our overall evaluation of the hematological effects of 7.5% NaCl/6% Dextran-70 (HSD), we have previously reported that infusion of 4 ml/kg HSD in hemorrhaged animals did not adversly affect clotting times or platelet aggregation, nor did it interfere with typing and cross-matching of red blood cells (RBC).

Methods: To present the blood picture following hemorrhage and HSD infusion more completely, the present study reports complete blood count (CBC) analysis and RBC morphology in rabbits (5-6/group) and pigs (8-11/group) infused with HSD. In addition sedimentation rates of erythrocytes (ESR) were determined in swine using Wintrobe tubes according to standard clinical laboratory procedures. Blood was obtained from euvolemic and hemorrhaged rabbits and pigs at times up to 7 d after infusion of 4 ml/kg HSD. Rabbits were hemorrhaged at 8 ml/kg and pigs were hemorrhaged at 27 ml/kg. A third group of pigs (n=6) were hemorrhaged and untreated. CBCs and platelet counts were determined, and qualitative RBC morphology was evaluated.

Results: In both species changes in hematocrit, hemoglobin, RBC, and platelet counts reflected the extent of hemorrhage and the subsequent plasma volume expansion induced by HSD. Infusion of HSD induced only minor variation in mean corpuscular volume, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration; findings consistent with the observed lack of significant morphological changes in RBC size, shape and staining intensity. In hemorrhaged swine, no significant differences in these variables were detected between untreated and HSD-infused animals at any time point. ESR increased with hemorrhage, but no additional HSD-induced effect was observed. Interestingly, a transient increase in white blood cell (WBC) counts was seen, and at 2 to 4 hr after hemorrhage, a marked increase in segmented neutrophils was observed in all groups of swine.

Conclusion: In general, no additional HSD-induced anemia was detected, and the observed effects on WBCs reflect more the response to hemorrhage and animal handling than effects of HSD. Thus, these data support other observations that HSD infusion should have minimal effects on hemostasis.

TREATMENT OF UNCONTROLLED HEMORRHAGE WITH HYPERTONIC SALINE (NaCl 8.0%): EFFECTS OF INJURY AND TREATMENT ON SELECTIVE ABDOMINAL ARTERIAL *vs* VENOUS INJURY.

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Background: Small infusions of Hypertonic Saline (HTS) has been shown to restore cardiovascular function in models of controlled hemorrhagic hypotension, however its safety in an uncontrolled bleeding situation has been disputed. The purpose of this study was to determine whether differences in the response to HTS treatment of hemorrhagic shock is attributable to the type of vessel lesioned.
Methods: Uncontrolled bleeding by selective abdominal vessel injury was produced on male WKY rats 17-21 weeks (330-420 gm) under general (α-chloralose) anesthesia. In group (A), the *aorta abdominalis* was punctured 3 mm proximal to the bifurcation using a 21g, 22g or 23g standard syringe needle. In group (V), the *vena cava inferior* was punctured 3 mm distal to to the renal vein entrance point using a 18g or 19g needle. Uncontrolled bleeding into the abdominal cavity commenced, and animals were turned on their sides. After 10 min, subjects were randomized to treatment with a small infusion of HTS (0.2 ml NaCl 8.0% /100 gbw, infusion rate 0.4 ml/min; groups AHTS and VHTS), or to no treatment to serve as controls (groups ACTR and VCTR). Subjects were observed for 240 min. Mean arterial pressure (MAP), heart rate (HR), and plasma-Na^+, -K^+, -glucose, -albumin and -total protein was recorded, as well as survival time.
Results: Syringes of different gauge were used to produce hemorrhage, but this had no influence on the recorded hemodynamic parameters (HR, MAP) before or after treatment, or survival time. Hypotension (mean and minimum MAP during the first 10 min after vessel puncture) was the same in all animals when groups were compared (ANOVA). Half of the animals (10 out of 21) with arterial hemorrhage died during the first 180 min after vessel puncture, while those surviving had a MAP of 68 mmHg or higher at the end of the observation period. Only 1 out of 17 animals with venous hemorrhage died during the observation period, and all survivors had a MAP of 68 mmHg or higher. When survivors and non-survivors were grouped and compared (irrespective of lesion site or treatment), there was a significant difference between these groups with respect to mean MAP the first 10 min after vessel puncture (before treatment). HTS treatment was not deleterious as long as mean MAP 0-10 min after puncture was above 25 mmHg, in which case all untreated subjects also survived. However, HTS treatment did not improve the outcome for subjects with MAP below 22 mmHg, in which case all untreated subjects also died.
Conclusions: The outcome of uncontrolled arterial hemorrhage may be less favorable than bleeding from a comparable venous injury (judged by equal drop in blood pressure and equal MAP after lesion). The single, most important factor in determining 240 min survival after intra-abdominal vessel lesion in this study was the initial drop in blood pressure, as reflected by MAP 0-10 min after vessel puncture. The outcome for either group (A) or (V) was independent of whether HTS treatment was given. We could not confirm evidence that HTS worsens the outcome of uncontrolled intraperitoneal hemorrhage. In the instances where the outcome was not predictable by MAP during the first 10 min, this might be attributed to the influence of factors other than HTS treatment, such as continued bleeding, rebleeding, or other shock parameters. From our study, we cannot conclude that there is a difference in response to HTS treatment between arterial and venous lesions.

ROLE OF GLUCOSE AND AMINO ACIDS IN 2400 MOSM ISOSAL: OSMOTIC SHIFT OF SODIUM FREE WATER

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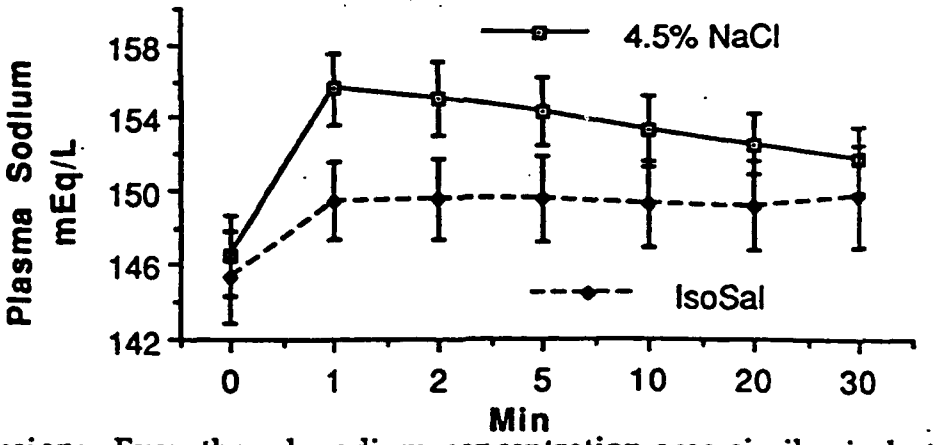
Background: IsoSal, a 2400 mosm hypertonic solution, has been shown to be effective in resuscitating hemorrhage in both the pediatric pig and adult sheep. IsoSal contains 4.5% NaCl, 5.9% glucose, and 6.3% mixed amino acids (Travasol). The concentration of NaCl in this solution is 4.5% compared to 7.5% NaCl used in conventional hypertonic saline formulations (HSD: 7.5% NaCl/6% dextran 70). With IsoSal resuscitation of hemorrhage, there is a marked reduction in the elevation of plasma sodium thus allowing larger volumes of this solution to be administered in situations where hypernatremia is of concern such as in the infant or pediatric patient. The current study was designed to evaluate the osmotic shifting capacity of the non ionic components of IsoSal, glucose and amino acids.

Methods: Sheep were surgically instrumented with catheters in the aorta, jugular vein, and a thermodilution pulmonary artery catheter. They were allowed 3-5 days to recover from the surgery before any experiments were performed. Six euvolemic sheep were studied in paired studies. Two solutions were tested, 4.5% NaCl (HS) and IsoSal. A bolus infusion of 4 ml/kg of the test solution was given after collecting baseline samples. Blood samples were collected for measurement of plasma electrolytes and osmolality over 30 min. Sheep were allow a minimum of 4 days before the alternate solution was tested.

Results: Peak plasma sodium only increased 2.8% with IsoSal compared to 6.2% with HSD. Plasma osmolality increased only 4.9% with HS compared to 9.4% with IsoSal. Results are shown for plasma sodium in the following graph:



Conclusion: Even though sodium concentration was similar in both solutions, the non ionic solute in IsoSal shifted significant fluid limiting the peak sodium increase. The greater osmolality of IsoSal shifted sodium free water into the interstitial space diluting the sodium load.

THE EFFECT OF HYPERTONIC SALINE/DEXTRAN ON CEREBRAL EDEMA AFTER EXPERIMENTAL BRAIN INJURY AND HEMORRHAGIC SHOCK

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Background: Experimental studies of our laboratory have shown that the infusion of 7.2% NaCl/10% Dextran 60 (HHS) has no adverse effects on cerebral blood flow and O2-supply of the brain in the presence of a focal brain injury. Further, HHS was shown to instantanously decrease elevated intracranial pressure after experimental brain injury and implantation of an epidural balloon. The present study was carried out in rabbits to analyze the effects of HHS on posttraumatic brain edema.
Methods: HHS (4ml/kg b.w.) was infused in anesthetized albino rabbits subjected to cryogenic brain lesion in combination with hemorrhagic shock. Brain edema was quantitatively assessed 4 hrs after trauma by specific gravity (SG) of multiple samples of grey and white matter.
Results: After sham operation SG was 1.03904 g/cm3, or 1.03448 g/cm3, respectively, in samples of grey and white matter of the traumatized cerebral hemisphere. Cold injury without treatment was associated with a significant increase of tissue water content in cortex (SG 1.03665 g/cm3) and underlying medulla (SG 1.0321 g/cm3). Treatment with HHS attenuated formation of brain edema in the traumatized hemispheres of all experimental groups and at all distances from the trauma.
Conclusion: The data demonstrate that HHS given as a shock treatment does not enhance but rather inhibit formation of posttraumatic brain edema. Even in areas close to the focal cerebral lesion, where the blood-brain-barrier is damaged, HHS administration was associated with a decrease of cerebral water content. Thereby, concerns are quenched that this form of shock treatment might be deleterious for the injured brain. Taken together with data from our previous studies we conclude that the prompt reestablishment of the general circulation by HHS does not pose a risk for the brain in severe head injury. To the contrary: Cerebral ischemia as a major mechanism of secondary brain damage in head injury is limited due to the improvement of cerebral O2-supply and the reduction of posttraumatic cerebral edema.

META-ANALYSIS OF SURVIVAL FOR PREHOSPITAL RESUSCITATION OF HYPOTENSIVE PATIENTS WITH HYPERTONIC/HYPERONCOTIC SOLUTIONS

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Background: Animal studies have shown that hypertonic/hyperoncotic solutions dramatically resuscitate animals from hemorrhagic shock and can significantly reduce intracranial water content and attenuate increases in intracranial pressure. The challenge for clinical trials is to determine whether these effects can translate into improved survival in patients.
Methods: We conducted a meta-analysis of survival for 618 patients enrolled into three randomized, double-blinded, controlled trials evaluating the use of hypertonic/hyperoncotic solutions for prehospital resuscitation of trauma patients undergoing ground ambulance and helicopter transport. Hypotensive patients were randomized to treatment with a 250 ml infusion of either isotonic crystalloid (IC), 7.5% NaCl (HS), or 7.5% NaCl/Dextran 70 (HSD). Neurologic impairment was defined as a Glasgow Comma Scale (GCS) score ≤ 8 at the time of entry into the study.
Results: The table gives the survival to hospital discharge for the entire cohort and for patients with GCS score of 8 or less.

	Treatment Group		
	IC	HS	HSD
Survival			
Entire cohort (n=618)	67% (n=212)	76% (n=135)	63% (n=271)
GCS score $\leq$ 8 (n=263)	27% (n=88)	40% (n=47)	35% (n=128)

Conclusions: Survival in the HS group tended to be higher for the entire cohort and for those patients with a GCS score $\leq$ 8. The addition of dextran was of no benefit. While prospective identification of severe brain injury is problematic in the field setting, a GCS score $\leq$ 8 does identify those patients at high risk for mortality. Definitive demonstration of statistical significance between IC and HS in patients will require a larger trial of at least 300 patients with an entry GCS score $\leq$ 8.

HYPERTONIC SALINE DEXTRAN ADMINISTRATION CAN BE DELAYED AFTER CRYSTALLOID RESUSCITATION FROM BURN INJURY

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Background: Previous studies by us showed that hypertonic saline dextran (7.5 NaCl in 6% dextran 70) given postburn (4 ml/kg) improved cardiac performance and reduced the total fluid requirements in guinea pigs. While these data confirm the cardioprotective effects of HSD immediately postburn, prehospital and early inhospital management of severely burned patients consists of aggressive crystalloid fluid resuscitation to correct intravascular volume deficits. The question arose as to whether delaying HSD for several hours after initiating crystalloid resuscitation would provide cardioprotection.
Methods: Third degree scald burns comprising 43±1% of the total body surface area (burn groups, N=40) or 0% for sham burn controls (Group 1, N=12) were produced. In Groups 2, 3, 4 and 5, Ringer's lactate (RL) was initiated, Parkland formula, 4 ml/kg/% burn. In Group 2, (N=12), RL was continued for 24 hours. HSD was administered as an IV bolus at either one hour (Group 3, N=10), four hours (Group 4, N=9), or eight hours postburn (Group 5, N=9); immediately after HSD administration, RL was continued (1 ml/kg/% burn) until 24 hours postburn.
Results:Compared to shams, hearts from burns treated with RL alone had cardiac dysfunction (LVP, 86.3±1.8 vs 61.6±2.9 mmHg, p=0.01; +dP/dt max, 1365±43 vs 1109±44 mmHg/sec, p=0.01; -dP/dt max, 1184±31 vs 881±40 mmHg/sec, p=0.01), a downward shift of left ventricular function curves from those calculated for sham burns, and lower LVP and ±dP/dt responses to increases in coronary flow rate. Compared to hearts from RL treated animals, hearts from burned animals treated with HSD one hour (HSD-1) and four hours (HSD-4) after burn injury had significantly higher LVP (RL: 62±3; HSD-1: 78±3, HSD-4: 68±3 mmHg, p<0.01) +dP/dt max, (RL: 1109±44; HSD-1, 1321±73; HSD-4: 1276±65 mmHg/sec, p=0.01) and -dP/dt max (RL: 881±40; HSD-1: 1151±101; HSD-4: 1048±63, p=0.01). Ventricular responsiveness for HSD-1 and HSD-4 groups to increases in preload and in coronary flow were comparable to responses documented in sham burn controls. Delaying HSD administration until eight hours after burn injury provided little cardioprotection.
Conclusion: Our data indicate that the time of HSD administration after burn injury is critical; HSD, given as a pharmacologic intervention with Ringer's lactate resuscitation, effectively maintains cardiac function and reduces overall total fluid requirements if administered within four hours after burn injury.

THE EFFECT OF 7.5% NACL/10% HYDROXYETHYL STARCH ON THE INTESTINE AFTER SUPERIOR MESENTERIC ARTERY OCCLUSION

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Background: Postischemic reperfusion of the intestine causes shock with deterioration of hemodynamic conditions and consequences for the whole organism. Aim of the study was to investigate the effect of hyperosmolar -hyperoncotic solution on the global circulation and on the intestinal postischemic microcirculation after temporary occlusion of the superior mesenteric artery in pigs.

Methods: After anesthesia of pigs (19-23 kg, 8-9 weeks old) catheters were inserted into the superior vena cava (central venous pressure), into the abdominal aorta (blood pressure) and into the superior mesenteric vein (blood gas analysis). A thermodilution catheter was placed into the pulmonary artery (cardiac output). An ultrasonic flowmeter was positioned around the superior mesenteric vein. Intestinal intramural pH was measured tonometrically in the proximal part of the ileum. Laser-Doppler flowmetry (LDF) was performed at a fixed loop of the ileum. The superior mesenteric artery was clamped for 2 hours in all animals with 2 hours reperfusion. Group 1 (n=6) received no therapy. In group 2 (n=6) hyperosmolar-hyperoncotic solution using 7.5%NaCl/10 hydroxyethyi starch 200000/0.5 (5 ml/kg) was injected within 5 minutes after onset of reperfusion.

Results: During ischemia both groups showed an increased systolic blood pressure (+6-32 mm Hg), a decrease of cardiac output (-15-25%) and of the intramural pH of the small intestine (pH 6.85-7.08; p=0.004). After onset of reperfusion in group 1 systolic blood pressure decreased for 40-60 mm Hg with a further deterioration of cardiac output to 40% of control. Intestinal intramural pH recovered only partially. LDF-values were reduced during ischemia and returned to subnormal levels during reperfusion with a significantly increased percentage of low flow areas (<15 LDF-units). With hypertonic-hyperoncotic treatment (group 2) systolic pressure and cardiac output were significantly better during reperfusion. Intramural pH returned back to normal within 30 minutes of reperfusion. In the initial phase of reperfusion microcirculatory hyperperfusion showed a significantly lower percentage of low-flow-areas, which returned to normal values at the end of reperfusion.

Conclusions: The use of hyperosmolar-hyperoncotic solutions ("small volume resuscitation") in the initial phase of reperfusion shock after intestinal ischemia improves hemodynamic conditions with a quick normalization of intramural pH, and an initial microcirculatory hyperperfusion with significantly less low-flow-areas.

HYPERTONIC SALINE ENHANCES CELLULAR IMMUNE FUNCTION

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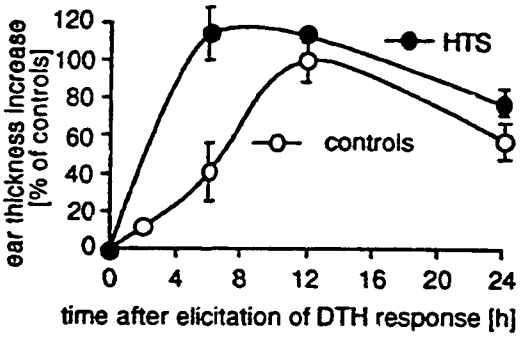
Background: Trauma results in severe suppression of immune function. Hypertonic saline (HTS) resuscitation improves outcome after trauma. We studied the effect of HTS on immune function to determine if improved outcome may be attributed to improved immune function.
Methods: Different HTS concentrations were used to test the effects of elevated extracellular sodium chloride levels on the proliferation of mitogen-stimulated peripheral blood mononuclear cells (PBMC) and LPS-stimulated monocyte TNF production *in vitro*. The effect of HTS on *in vivo* cell-mediated immune function was tested using 6 New Zealand white rabbits. Delayed-type hypersensitivity (DTH) reaction to 2,4,6-trinitrochlorobenzene (TNCB) was measured in 3 animals injected with 10 ml/kg 7.5% NaCl in Ringer's solution and in 3 control animals injected with an equal volume of Ringer's solution. This HTS concentration resulted in an increase of plasma Na^+ to levels comparable to those reached after HTS resuscitation of trauma patients (10-20 mM for at least 8 hrs).
Results: *In vitro* T-cell proliferation of human and rabbit PBMC was doubled at 25 mM increased extracellular Na^+ concentrations. Further increased hypertonicity (>40 mM with human cells, >80 mM with rabbit cells) caused progressive suppression of proliferation. Human and rabbit monocyte functions (TNF production) was augmented by 300% at 30 mM hypertonicity, indicating that HTS-enhanced accessory cell function of monocytes may cause increased T-cell proliferation.



Substitution of HTS with KCl also enhanced *in vitro* T-cell proliferation, suggesting that osmotic effects may be involved in the mechanisms responsible for up-regulating immune cell function.
HTS injection in healthy rabbits increased cell-mediated immune function (delayed-type hypersensitivity reaction) indicating that HTS may not only enhance *in vitro* but also *in vivo* cellular immunity (see figure).
Conclusion: Our findings suggest that increased plasma osmolality after HTS resuscitation may up-regulate cellular immune function. HTS resuscitation of trauma patients results in elevated plasma Na^+ concentrations to levels that significantly enhanced immune functions in our experiments. Further experiments should determine if HTS resuscitation may serve as a useful tool to reduce post-traumatic immunosuppression and prevent the risk of septic complications following trauma.

ROLE OF HISTAMINE RECEPTORS AND ENDOTHELIUM IN CARDIAC CONTRACTILITY CHANGES FOLLOWING HYPERTONIC SALINE INFUSION

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Background: Small volumes of hypertonic (7.5 %) saline (HS) applied for resuscitation from hypovolemia effectively restore cardiovascular function and have a vasodilator effect. Cardiac tissue contains a large amount of histamine (HIS), an autacoid with inotropic and vasodilator effects. Recently it has become evident that the endothelium represents a complex, dynamic organ with diverse functions, including the synthesis and release of vasoactive agents such as the endothelium derived relaxing factor (EDRF/NO) or HIS. In a previous study (SALT 5) we demonstrated an elevation in plasma HIS level and HIS synthesis in cardiac tissue simultaneously with an increase in cardiac contractility after a 4 ml/kg HS infusion. The present study sought to examine whether HIS could possibly play a role in the vasodilatation and increased cardiac contractility observed after HS infusion. In addition, we have studied the role of EDRF/NO in these responses.

Methods: The experiments were performed on pentobarbital-anesthetized normovolemic open-chest mongrel dogs of both sexes. Mean arterial pressure (MAP), central venous pressure, cardiac output (CO, thermodilution) and hematocrit were measured and total peripheral resistance (TPR) was calculated. Left ventricular contractility (LVC) was estimated from the end-systolic pressure-diameter (ESPD) relationship by monitoring left ventricular pressure (LVP) with a catheter-tip micromanometer and left ventricular diameter (LVD) with a pair of ultrasonic crystals sutured on the myocardium. Pressure-diameter loops were obtained during transient vena caval occlusions with a balloon catheter. The slope of the ESPD relationship was calculated with a computer program. The animals were divided into four groups. In the control group (Group 1) 4 ml/kg HS was infused iv for 15 min. In Groups 2 and 3, the animals received 2 mg/kg of the H_1-blocker tripelennamine and 2 mg/kg of the H_2-receptor antagonist ranitidine before HS infusion, respectively. In Group, 4 the animals were pretreated with 2 mg/kg NG-nitro-L-arginine (NNA) to inhibit the synthesis of the EDRF/NO.

Results: Infusion of corresponding volumes of 0.9 % NaCl had no effect on the measured variables. A transient increase in MAP, LVP and CO and a decrease in TPR and hematocrit was observed after HS infusion. In the control group an increase in LVC (from 26.6 to 41.7 mmHg/mm) occurred lasting about 30 min. The H_1-blocker tripelennamine significantly inhibited the HS-stimulated LVC. Ranitidine pretreatment did not affect the increase in LVC after HS infusion. Inhibition of EDRF/NO synthesis caused an elevation in basic LVC, but HS administration did not increase LVC after NNA pretreatment.

Conclusion: 4 ml/kg HS infused into dogs causes a release of HIS detectable in the plasma. The endothelial autacoids, EDRF/NO and HIS could play a role in the decrease in TPR and elevation of LVC following hypertonic resuscitation. It seems that the HIS effect occurs via the H_1-receptors.

IN VITRO STUDY OF ENDOTHELIUM DEPENDENT HISTAMINE RELEASE FROM CANINE MESENTERIC ARTERIAL SEGMENTS

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Background: Recently it has become evident that the endothelium represents a complex, dynamic organ with diverse functions, including the synthesis and release of vasoactive agents. These mediators (EDRF, prostacyclin and histamine) can induce significant vascular smooth muscle relaxation causing increases in blood flow. In a recent study from our laboratory, a release of histamine was demonstrated in the effluent blood from a canine ileal segment during reperfusion following 30 min of ischemia. In another experimental series an elevation of plasma histamine level was shown following hypertonic saline infusion. However in these experiments the source of histamine liberation was not clear. The aim of the present study was to examine whether an endothelial histamine liberation occurs in vitro from mesenteric arterial segments in response to an increased shear stress (elevated flow velocity) or administration of hypertonic saline.
Methods: An ileal artery segment (average length 3 cm; diameter about 1 mm) was cannulated at both ends, dissected out and mounted in a 1 ml organ chamber. It was perfused with a constant flow (5 ml/min) at 37 ^{o}C with Krebs-Henseleit solution containing 0.1 mM histidine. Input perfusion pressure (IPP) was monitored and the histamine level in the effluent was determined (radioenzymatic method). We performed two experimental series. In Series I we examined the effects of increased flow rate (16 ml/min) or administration of hypertonic Krebs solution (HKS, containing 180 mM NaCl) on histamine release. The duration of both stimuli was 10 min. In Series II the endothelium was damaged by luminal perfusion of a ten-fold diluted Krebs solution and the above series was repeated. The endothelium dependent relaxation was assessed with test doses of acetylcholine (ACh, 10^{-9}-10^{-7} M) before and after endothelium damaging.
Results: In the presence of an intact endothelium the higher flow rate and administration of HKS increased the IPP and caused a 3-fold and 2-fold elevation in the histamine level of effluent, respectively. In Series II the endothelium dependent relaxation in response to ACh test doses decreased significantly. In the case of damaged endothelium neither of the stimuli elevated significantly the basal histamine release despite an increase in IPP.
Conclusion: Our results suggest the significance of endothelial cells in histamine liberation after hypertonic resuscitation. The increased shear stress (elevated flow velocity) may stimulate histamine synthesis in the endothelium. The endothelium-derived histamine may have a role local vascular regulation.

INITIAL RESUSCITATION OF BURN INJURY WITH HYPERTONIC SALINE DEXTRAN (HSD) PREVENTS THE REVERSAL OF THE PLASMA-INTERSTITAL ONCOTIC GRADIENT IN NON-BURNED SKIN

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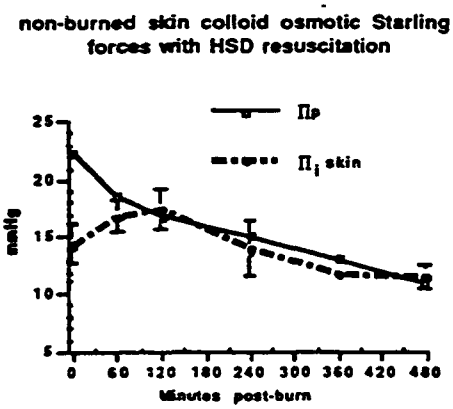
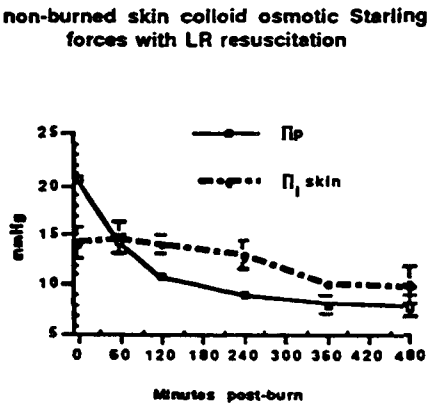
Fluid resuscitation of large thermal injury reduces the plasma oncotic pressure (Πp). Furthermore, a systemic-wide increase in capillary permeability raises the interstitial colloid osmotic pressure (Πi) and reverses the Πp-Πi gradient in tissue not directly injured. In the present study, we compared isotonic and hypertonic resuscitation of burn injury and the effects on the Πp-Πi gradient. Anesthetized sheep (35–45 kg) were given a 85°C, 85% BSA partial thickness scald. Initial resuscitation was with 10 ml/kg lactated Ringer's (LR) or 7.5% hypertonic saline 6% dextran (HSD). The solutions were infused "blindly" at a rate just sufficient to restore baseline oxygen delivery; after test fluid administration all animals were supported on LR to maintain the same baseline DO_2. The Πi was measured with a tissue oncometer and dermal biopsies from non-burned skin. Πp was measured with plasma samples from the same time point. HSD reduced the 8 hr volume requirements by 76±5%. The 10 ml/kg HSD infusion lasted 280±22 min while, the 10 ml/kg LR infusion lasted only 33±6 min. A reversal of the Πp-Πi gradient occurred within the first hr with LR due to a large fall in Πp, while HSD ameliorated the fall in Πp. The Πi, however, was initially elevated in the HSD treated group but it was not significantly different from the LR group. Elevation of the Πi may reflect a greater leakage of colloid into the interstitium of the non-burned skin. Initial resuscitation of burn injury with HSD maintains Πp better due to a higher plasma protein as well as the direct oncotic effects of dextran.





HYPERTONIC SODIUM ACETATE TREATMENT OF UNCONTROLLED HEMORRHAGIC SHOCK (UCHS) IN AWAKE RATS.

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Background: Hypertonic sodium acetate has been recently suggested for treatment of hemorrhagic shock. In the present study the effectiveness of hypertonic sodium acetate and hypertonic saline in UCHS was compared in awake rats.
Methods: Twenty four hours prior to the experiment the animals were cannulated under general anesthesia. UCHS was induced by injury to 2 major branches of the ileo-colic artery to induce arterial bleeding . The animals were than randomly divided into 4 groups : gr.1(n=8) was untreated. gr.2(n=8) was treated after 10 minutes with 5ml/kg 7.5% NaCl (HTS). gr.3 (n=8) was treated with 5ml/kg 9.2% CH_3COONa in 0.9% NaCl (ACE). gr.4 (N=8) was treated with 41.5 ml/kg 0.9% NaCl (Large volume normal saline = LVNS).
Results: Arterial bleeding in gr.1 was followed by a fall in mean arterial pressure (MAP) from 100~3.2 to 86~7.1 mmHg ($p<0.001$), pulse rate increased from 506~30 to 566~26 per minute ($p<0.005$) and hematocrit decreased from 42~1.2 to 36~1.5 percent ($p<0.01$) in 10 minutes. A similar response was observed on all 4 groups. Infusion of HTS was followed by a further fall in MAP to 47~8.2 mmHg ($p<0.01$) and infusion of ACE was followed by a fall in MAP to 51~4.3 mmHg ($p<0.01$) after 60 minutes. In the untreated gr.1 MAP decreased to 63~5.3 mmHg after 60 minutes which was significantly higher than in gr.2 ($p<0.05$) and gr.3 ($p<0.05$). Infusion of LVNS in gr.4 was followed by a fall in MAP to 61~4.6 mmHg after 60 minutes which was similar to the rsponse in the untreated group. The mortality rate after 4 hours was 25% in gr.1 and gr.4, 50% in gr.3 ($p<0.05$) and 75% in gr.2 ($p<0.01$).
Conclusions: Hypertonic saline and hypertonic sodium acetate infusion in uncontrolled hemorrhagic shock in awake animals lead to increased bleeding from injured vessels, fall in MAP and increased mortality while the response to large volume normal saline (LVNS) is similar to untreated animals.

HYPERTONIC SALINE RESUSCITATION OF UNCONTROLLED ABDOMINAL VISCERAL HEMORRHAGE

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Background: Uncontrolled hemorrhage models of major vessel injury suggest that fluid therapy is dangerous prior to definitive control of bleeding. Hypertonic solutions are particularly implicated because small volumes rapidly increase blood pressure. Major vessel injury models are most analogous to penetrating injury. We studied uncontrolled hemorrhage in a model more typical of blunt trauma: parenchymal liver injury. Methods: Rat femoral vessels were cannulated. Celiotomy was performed and 65% of two lobes of the liver removed. No attempt was made to control hemorrhage and the incision was closed. A control group was not resuscitated (NR). Resuscitation was begun 15 minutes post-injury in 3 other groups: small volume lactated Ringer's (SVLR, 4 ml/kg), large volume lactated Ringer's (LVLR, 24 ml/kg), and 2,400 mosm/l hypertonic saline (HS, 4 ml/kg). Fluids were given at 0.4 ml/min. Mean arterial pressure (MAP) was followed for 240 min. At sacrifice, the abdomen was reopened and shed blood volume measured. Controlled hemorrhage experiments were also done to estimate circulating blood volume. Results: Before resuscitation, MAP fell to 20-30 mmHg. and mortality was 20%. Below are values for MAP at different times, abdominal blood volumes, estimates of circulating blood volume, and group mortality (Mean ± SEM, ANOVA):

	MAP (mmHg)			Abd. Blood	Circ. Vol	Mortality
	20 min	45 min	240 min	(ml/kg)	(ml/kg)	
NR (n=11)	58±6	76±5	76±4	18.8±0.7	49.9±0.7	2/11
SVLR (n=11)	71±7	78±4	74±3	20.2±0.9	50.6±0.9	1/11
LVLR (n=11)	64±7	74±7	63±5	25.1±0.7#	45.2±0.7*	1/11
HS (n=12)	97±8	102±7	92±5	23.5±0.9#	48.6±0.9	1/12

* $p<0.05$ vs other 3 groups; # $p<0.05$ vs NR and SVLR

Conclusions: 1. Vigorous volume resuscitation increases bleeding from uncontrolled parenchymal liver injuries. 2. Hypertonic saline better supports blood pressure than does large volume isotonic crystalloid. 3. Estimates of circulating blood volume suggest that large volume isotonic resuscitation depletes the intravascular space more than other resuscitation regimens. These results should be confirmed with direct measurements of circulating volume.

EARLY, LOW-VOLUME HYPERTONIC SALINE-DEXTRAN RESUSCITATION FOR THERMAL INJURY.

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Background: Hypertonic saline-dextran (HSD) has been proposed for low volume resuscitation from hemorrhage in the pre-hospital setting when IV access may be difficult. Patients with large burns also have problems with IV access, and hypotension. We compared a burn resuscitation using HSD vs. NS for the first hour.

Methods: 16 chronically instrumented sheep were subjected to a 33% scald burn under anesthesia after a 1 hr baseline determination. All animals were conscious within 30–40 min after burn injury, and given prn analgesics after recovery. After no resuscitation for 1 hr to allow development of burn shock, 4cc/kg of NS or HSD (6% NaCl/7.5% dextran 70) was infused blindly over 1 hr. Resuscitation was continued with RL, titrated to maintain cardiac output (CO) within 10% of baseline. Cardiovascular parameters were measured hourly for 12 hrs and then every 4 hrs. At 24 hrs the animals were sacrificed and tissue samples obtained for water content.

Results: All animals were able to be resuscitated with the formulas as above. The following table demonstrates the comparison of cardiac output two hours after burn injury, amount of fluid required to resuscitate the animals over the first 8 hours after injury and over the entire 24 hours, and the maximal serum sodium obtained.

	CO (2hrs)	input (cc/kg/%burn) 0-8 hrs	0-24 hrs	Na^+ (max)
HSD (8)	97%*	1.55 ± 0.24*	4.10 ± 1.5	167 ± 7*
NS (8)	73%	1.91 ± 0.21	5.44 ± 1.5	159 ± 5

*$p<0.05$

Conclusion: HSD infusion produced improved CO compared to NS, and fluid requirements were significantly decreased for the 1st 8 hrs. Serum Na^+ was elevated with HSD but normalized during the experiment; hypernatremia was not a problem. Tissue water content at 24 hrs was equivalent. Early HSD resuscitation rapidly stabilizes the thermally injured patient.

HYPERTONIC SALINE/DEXTRAN PRIME FOR CARDIOPULMONARY BYPASS REDUCES OVERALL FLUID BALANCE AND GUT TISSUE WATER

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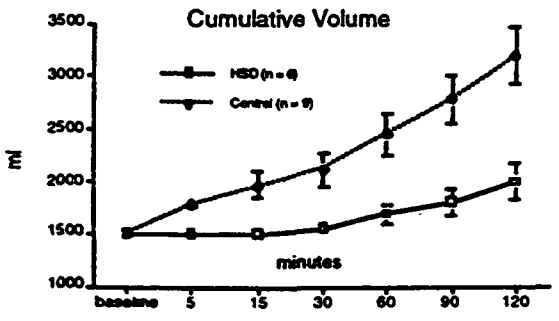
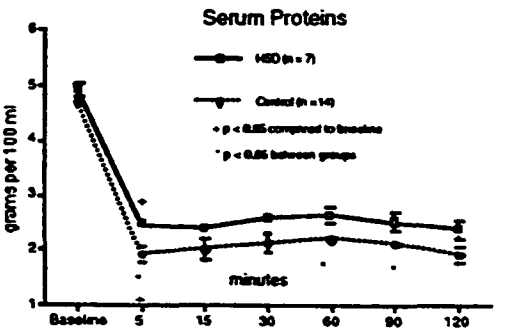
Background: Fluid retention is a common postsurgical complication of cardiopulmonary bypass (CPB). Hypertonic saline dextran (HSD) has been shown to lower volume requirements when used as a treatment for hypovolemia. We evalutated the effectiveness of adding HSD to the pump prime during experimental CPB.
Methods: Immature female swine weighing 26 to 39 kg underwent two hrs of CPB. Perfusion consisted of an asanguinous prime (1 liter Plasmalyte (PLA) and 500 ml 6% Hetastarch), nonpulsatile flow (100ml/kg/min), membrane oxygenator with open venous reservoir, a 40 μ arterial line filter, normothermia (37°C), and an empty beating heart. The experimental group (HSD) received a 1 ml/kg dose of hypertonic saline/dextran (25% NaCl and 24% dextran 70) in the prime. The control group received the same volume of lactated Ringer's (LRS). Additional PLA was infused as needed to maintain pump reservoir volume at a predetermined level during CPB.
Results: There were no differences in hemodynamics (pressures in aorta, right atria, and pulmonary artery, peripheral resistance; hematocrit; urine output) between groups during the experiment. Plasma sodium levels were significantly higher in the HSD group (159.7 ± 17.0 vs. 140.2 ± 1.9) five minutes after CPB was initiated ($p<.05$), while at the end of bypass serum sodium in the HSD group had fallen to (144.6 ± 2.7) and the LRS group remained essentially the same (139.9 ± 2.6). Colloid oncotic pressure (COP) was significantly higher in the HSD group (12.1 ± 2.2 vs. 9.1 ± 1.9) at 120 minutes of bypass ($p<.05$). The HSD group required significantly less volume and resulted in significantly higher serum protein levels for CPB than the LRS group. Water content of all tissues tended to be less in the HSD group, but were significantly less in the duodenum (5.77 ± 0.46 vs. 8.81 ± 1.91), jejunum (5.21 ± 0.21 vs. 7.26 ± 0.65), and colon (3.83 ± 0.27 vs. 4.72 ± 0.23).





Conclusion: HSD as a prime additive significantly lowered exogenous fluid requirements and gut tissue water during CPB without changing hemodynamics. Both COP and serum proteins were maintained at higher levels during CPB, contributing to HSD's volume sparing effects.

HYPERTONIC SALINE IMPROVES CEREBRAL OXIDATIVE METABOLISM AND CYTOCHROME AA3 REDOX STATE DURING HEMORRHAGIC HYPOTENSION IN DOGS

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Background: Hypertonic saline used in the treatment of hemorrhagic shock dramatically improves cardiovascular performance. The aims of the present study are to observe how hemorrhagic hypotension affects cerebral oxygen metabolism and to determine whether hypertonic saline will improve the latter in relation to tissue oxyhemoglobin (HbO2), deoxyhemoglobin (Hb), total hemoglobin (total Hb, Hb+HbO2), and the redox state of mitochondrial cytochrome aa3 (Cyt aa3).

Methods: Fourteen mongrel dogs were randomly divided into two groups of seven. All were anesthetized by intravenous injection of pentobarbital 25 mg/kg body weight. Endotracheal intubation and mechanical ventilation was performed with room air at a rate suitable for maintaining 35-40 mmHg of PaCO2. Three cannulas were inserted, one into each femoral artery and one into the right femoral vein. The MAP, systolic arterial blood pressure, diastolic arterial blood pressure, heart rate and ECG were continously monitored. The right portion of each dog's head was thoroughly shaved and two optical probes were firmly taped on the scalp with black adhesive tape and wrapped with an opaque black cloth. The dogs were bled from the femoral artery over a period of 15 min by a modification of Wiggers method until their MAPs were 65 mmHg (in group H) or 45 mmHg (group L), which were maintained for a further 30 min by the removal or injection of blood. Then, 1.5 mL/kg of 20% hypertonic saline was injected to resuscitate the animals. The concentrations (μ M/L tissue) of HbO2, Hb, total Hb, and Cyt aa3 are automatically quantified by a microcomputer incorporated in the infrared spectroscope, using the Beer-Lambert law. The experimental data were processed by Student's t test and two-way variance analysis. Statistical significance was recognized at $P \leq 0.05$.

Results: Forty-five min of hemorrhagic hypotension led to decreases in cerebral HbO2 (from control level 0 to -25.5 ± 7.5 μ M/L brain tissue in group H and to -32.3 ± 7.5 μ M/L brain tissue in group L), in total Hb (from control level 0 to -7.2 ± 1.8 μ M/L brain tissue in group H and to -6.5 ± 1.7 μ M/L brain tissue in group L), and in oxidized Cyt aa3 in group L (from control level 0 to -0.8 ± 0.4 μ M/L brain tissue), but to increases in Hb (from control level 0 to 15.5 ± 5.0 μ M/L brain tissue in group H and to 25.8 ± 3.4 μ M/L brain tissue in group L) and in oxidized Cyt aa3 in group H (from control level 0 to 0.6 ± 0.3 μ M/L brain tissue). Hypertonic saline administration reversed these changes significantly, especially in group H, except for oxidized Cyt aa3 in group H.

Conclusion: 20% hypertonic saline can effectively improve cerebral oxidative metabolism disturbances induced by hemorrhagic hypotension.

INHIBITORY EFFECT OF HYPERTONIC SALINE ON THE DELAYED NEURONAL DEATH IN HIPPOCAMPUS CA1 AREA OF THE GERBILS SUBJECTED TO TRANSIENT GLOBAL ISCHEMIA

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Background: It is well known that hypertonic saline can greatly improve the hemodynamic in hypovolemic shock. This experiment was performed to evaluate whether hypertonic saline improves the delayed neuronal death in the hippocampus CA1 area of the gerbil brain.

Method: The bilateral common carotid arteries of gerbils (65-90 g) were occluded by clips transiently for 2.5 min under halothane anesthesia after ether induction. Following reopening of the bilateral common carotid arteries, 2 mg/kg of 10% NaCl (HSS) was injected via the tail vein. In control group, the same dose of physiological saline (PSS) was injected. After 5 days of spontaneous reperfusion, the brain was removed, sliced at 5 um thick, and the sections of hippocampus were observed by light microscope after they were fixed and stained by hematoxyline and eosin. The animals were randomly assigned to one of the four groups: Group 1, Sham operation + PSS.; Group 2, Sham operation + HSS; Group 3, Ischemia-reperfusion + PSS; Group 4, Ischemia-reperfusion + HSS.

Results: Group 1 and 2 revealed normal findings. Group 3 (Ischemia + PSS) revealed disappearance of the radial striatum and vacuolization, piknosis, death of the pyramidal neurons (about 80% were dead). In Group 4 (Ischemia + HSS), the radial striatum was manifested in normal figures and the pyramidal neurons were also almost normal.

Conclusion: Hypertonic saline is effective to alleviate the delayed neuronal death in hippocampus CA1 of the gerbils subjected to transient global ischemia.

FLUID SHIFTS FOLLOWING ADMINISTRATION OF 7% SODIUM CHLORIDE.

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Background: Hypertonic saline (HS) effectively improves blood pressure and cardiac output following hemorrhagic shock. Cardiac contractility is increased following HS; still, mobilization of interstitial (as well as intracellular) fluid has been assumed to be as important for the hemodynamic improvement. This study determined the effects on extracellular volume (ECV) and on interstitial fluid volume (IFV) and intracellular fluid volumes (ICV) in several tissues following HS administration.
Methods: In pentobarbital-anesthetized normovolemic rats, 7% NaCl (HS; 1.1 ml/100 g; 2400 mosmol/l) was administered i.v. over a 20 min period. Animals receiving either acetated Ringer's 10 ml/100 g (i.e., the same amount of sodium) or no fluid infusion served as controls. ECV was determined as the two-hour ^{51}Cr-EDTA space after nephrectomy. Further, in samples from skeletal muscle, skin, small intestine, liver, and lung, the local ECV and local plasma volume (as five-minute ^{125}I-albumin distribution volume) were determined. Interstitial fluid volume was calculated as the difference between ECV and local plasma volume. Changes in intracellular volume were determined from changes in local tissue water and ECV.
Results: ECV was 21.1±0.6 ml/100 g in control (mean±SEM; n=6). Following 7% NaCl, ECV increased to 26.1±0.4 ml/100 g ($p<0.05$). After Ringer infusion ECV was 32.8±0.5 ml/100 g ($p<0.05$).

Table: Fluid volumes in selected tissues

	Interstitial fluid volume		Intracellular fluid volume		
	HS	Control	HS	Control	
Muscle	376±16*	274±10	2410±25*	2631±26	µl/g DW
Skin	1193±36*	974±65	337±14	317±36	µl/g DW
Intestine	532±47*	376±56	592±62	546±89	µl/g DW
Liver	591±14	551±31	1396±10*	1558±39	µl/g DW
Lung	1353±40	1119±60	2124±150	2088±119	µl/g DW

Means±SEM; *, $p<0.05$ vs. Control; DW: dry tissue weight

Conclusions: The present study quantified alterations in ECV following HS infusion. HS increased ECV by 4-5 times the infused volume, resulting in a significant increase in interstitial volume in skin, muscle and intestine. A 10% reduction of intracellular volume was found in muscle and liver. Constituting a large fraction of the body, and with a large intracellular fluid volume, skeletal muscle seems to be the main reservoir for mobilization of intracellular fluid following infusion of hypertonic saline.

Supported by grants from The Research Council of Norway (102630/320), The Laerdal Foundation for Acute Medicine, and the Norwegian Air Ambulance.

THE EFFECT OF BLOOD AND SALINE TRANSFUSION FOLLOWING HEMORRHAGE ON NON INVASIVE MEASUREMENTS OF MICROCIRCULATORY HEMODYNAMICS

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Background: The aim of the study was to examine the hemodynamic response of the microcirculation to blood or saline transfusion following acute hemorrhage.
Methods: Ten rabbits were studied using simultaneous non invasive monitoring of subcutaneous flux, red blood cell amount and oxygenation, measured by Laser Doppler Flowmetry (LDF), Photoplethysmography (PPG) and Transcutaneous Oxygen Tension ($tcPO_2$) respectively. Following withdrawal of 25% of the total blood volume, a decline of $45 \pm 15\%$, $27 \pm 17\%$ and $45 \pm 15\%$ of baseline value was observed in these three parameters respectively. Blood (5 rabbits) or saline (5 rabbits) was administered and the following hemodynamic changes were observed:

Results:	%LDF	%PPG	%tc-PO_2
Blood return	103.2 ± 11.1	100 ± 16.2	110.6 ± 16.9
Saline return	75.0 ± 7.3	31.6 ± 8.0	76.4 ± 6.6
Significance	$p < 0.001$	$p < 0.0001$	$p < 0.030$

All values are calculated from baseline as % from pre-hemorrhage values.
Conclusions: These results demonstrate that blood or saline transfusion following hemorrhage have different effects on microcirculatory hemodynamics and the LDF, PPG and $tcPO_2$ may be very sensitive non invasive methods to monitor these changes.

HEMODYNAMIC EFFECTS OF SMALL VOLUME HYPERTONIC SOLUTIONS IN LOWER TORSO ISCHEMIA AND REPERFUSION IN HEMORRHAGIC SHOCK

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Background: Aortic occlusion (AO) is an essential maneuver in the treatment of severe hemorrhage from an abdominal vascular source. We have previously shown that hypertonic saline solutions significantly improve hemodynamic and metabolic profiles during aortic occlusion in severe hemorrhagic shock (Circ.Shock,37:7,1991; Circ.Shock, 42:8,1992). In order to evaluate the hemodynamic effects of a single bolus of small volume hypertonic solutions given just before lower-torso reperfusion of aortic balloon occlusion for hemorrhagic shock, we compared this procedure with others fluid resuscitation regimens.

Methods: Forty-eight pentobarbital anesthetetized dogs were submitted to pressure driven hemorrhage - PHD (Circ Shock,36:13,1992) for 30 min (average blood loss: 32 ml/kg), followed by transfemoral aortic balloon occlusion of the aorta at T10 level. Dogs were randomized into 6 groups, according to the single bolus injected at 55 min: **CT** = NaCl 0.9%, 4ml/kg; **IS32** = NaCl 0.9%, 32ml/kg; **IS3X** = NaCl 0,9%, 3 times the blood volume removed during PDH; **HSD** = NaCl 7.5%-6%Dextran70, 4ml/kg; **HAD** = Sodium acetate 10.5%-6% Dextran70, 4ml/kg; **SB** = reinfusion of the total volume of shed blood removed during PDH. Reperfusion started at 61 min.

Results: During PDH, all groups exhibited low mean arterial pressure (MAP), cardiac index (CI), O_2 consumption (VO_2) and availability (DO_2). aortic occlusion induced only MAP recovery; after reperfusion, **CT** animals had severe shock, 4 dying before the end of the experiment. All others groups exhibited mild hypotension on reperfusion, with increased CI, highest in **IS3X** group; DO_2 and VO_2 did not differ significantly among treated groups.

Conclusion: We conclude that a small volume bolus of hypertonic solutions, can produce immediate significant hemodynamic benefits, similar to large volume bolus of either isotonic solutions or whole blood, in the lower torso reperfusion after aortic declampnig in hemorrhagic shock.

MAP/CI(mmHg/l.min.m2)		**AO**		**FB**	**REP**			
	0'	**30'**	**45'**	**60'**	**65'**	**75'**	**90'**	**120'**
CT	120/2.6	31/0.6	106/0.8	115/1.2	46/1.2	41/1.1	41/0.9	47/0.8
IS32	108/2.9	28/0.7	108/1	129/6	70/3.7	71/3	75/2.1	61/1.7
IS3X	110/2.8	47/0.7	112/0.8	123/9.5	74/7.3	81/7	85/4.4	73/2.5
HSD	125/2.6	27/0.6	127/0.9	137/5.7	65/3.1	76/2.2	83/1.9	79/1.6
HAD	115/2.8	30/0.7	117/0.9	121/5.8	56/3.4	52/2.3	52/1.8	51/1.3
SB	104/2.4	25/0.6	106/0.7	149/3.2	76/2.4	89/2.1	92/1.8	84/1.4
DO_2/VO_2(ml/min.m2)								
	0'	**30'**	**45'**	**60'**	**65'**	**75'**	**90'**	**120'**
CT	399/122	86/56	100/60	150/60	149/73	143/77	121/81	117/71
IS32	469/125	111/72	152/53	507/83	367/98	320/119	247/110	216/105
IS3X	495/125	107/73	118/61	445/87	482/100	515/118	71/101	281/98
HSD	424/110	101/76	132/55	617/79	378/127	271/106	255/111	229/111
HAD	477/126	102/68	126/58	565/84	381/127	282/128	240/129	177/103
SB	365/100	91/60	103/53	492/87	393/107	333/107	310/113	272/109

AO: *aortic occlusion at 31';* **FB:** *fluid bolus at 55';* **REP:** *reperfusion at 61'*

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HYPERTONIC-HYPERONCOTIC SALINE SOLUTION FOR THE TREATMENT OF POST - TRAUMATIC HYPOTENSION IN THE EMERGENCY ROOM. THE BRAZILIAN MULTICENTER TRIAL

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Background: In order to evaluate the effects of the use of hypertonic-hyperoncotic solution as the first emergency room intravenous fluid for the treatment of post-traumatic hypotension, we started a multicenter trial in ten of the busiest trauma centers in Brazil.

Methods: The study will include victims of trauma that arrive in the emergency room with a systolic blood pressure of 90 mmHg or less. The exclusion criteria are (i) age under 16 years, (ii) associated burn injury, (iii) absence of carotid pulse or sinus rhythm on ECG, (iv) pregnancy and (v) presence of chronic disabling diseases.
This is a double-blinded prospective study in which the first intravenous infusion is a 250 ml coded solution, of either lactated Ringers or of 7.5% NaCl - 6% Dextran 70 (HSD) solution. The coded solution will be followed by the routine resuscitation procedure. The primary end-point is to determine the 24 hour and 30 day mortality. Secondary end-points are the incidence of complications, type and volume of fluid resuscitation and length of hospitalization. The patients shall be evaluated by R.T.S., A.I.S., I.S.S., and T.R.I.S.S. scores. Each center is expected to contribute 160 patients to the study. We therefore expect to include around 1600 patients during a one year period. Provisions have been made to brake the code instantly in the case of unexplained adverse reactions. Results shall be collected and analyzed by The Clinical Epidemiological Service of Escola Paulista de Medicina, São Paulo, Brazil.

Results: The trial began in January 1st, 1994. On April 15th, 1994, 125 patients have been entered. The rate of patient inclusion is below the expected level, but 4 centers were late in starting. General information on mortality and epidemiology of the trial shall be provided.

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CHANGES IN CEREBROSPINAL FLUID OSMOLALITY AFTER INTRAOPERATIVE VOLUME REPLACEMENT WITH HYPERTONIC-HYPERONCOTIC SALINE/DEXTRAN VS. RINGER'S LACTATE/GELATINE

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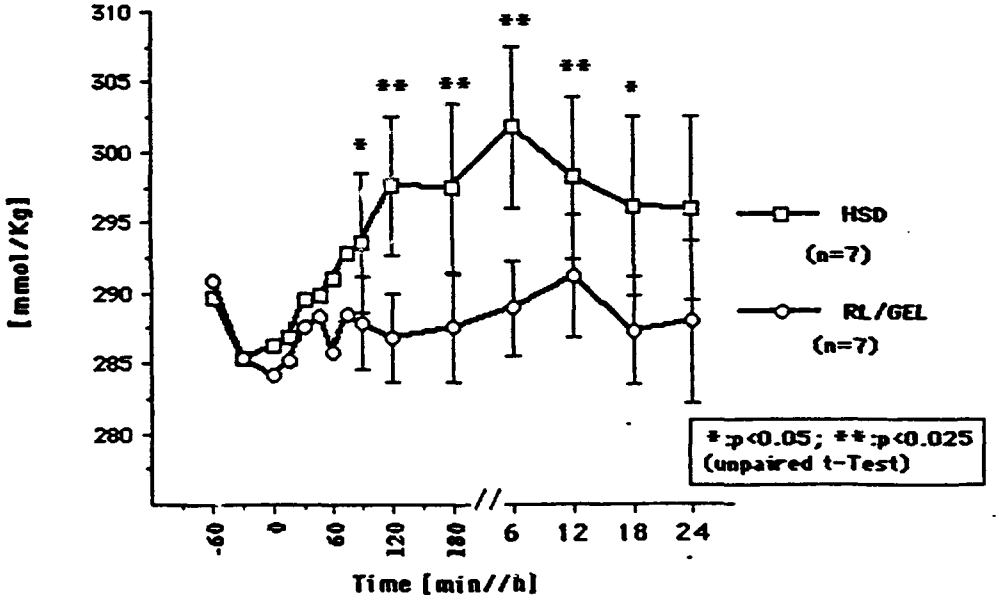
Background: One of the suggested mechanisms of action in small-volume resuscitation (SVR) is stimulation of the central vasomotor center. It has been shown that direct intraventricular infusion of hypertonic NaCl results in increased resistance to hemorrhage in sheep and in cardiovascular changes similar to those during SVR in dogs. Therefore, we examined alterations in cerebrospinal fluid (CSF) osmolality and sodium concentration during SVR.
Methods: 14 patients undergoing total hip prosthesis replacement in continuous spinal anesthesia were divided into two groups receiving either 4%-gelatine/Ringer's lactate (RL/Gel) or a bolus (4ml/Kg) of 7,5% NaCl/6% Dextran-70 (HSD) . Solutions were infused through a central venous catheter after a blood volume loss of 10% or a drop in baseline MAP of 15% (t_0). CSF was tapped from a catheter placed through a 16-G Touhy needle. CSF Na, Cl, K and osmolality were measured every 15 min. during the operation and at 6 hour intervals for 24 hours.
Results: The graph shows mean CSF-Osmolality +/- SD in each group.



Conclusion: 1) Hypertonic/hyperoncotic solutions are effective and safe for treatment of intraoperative hypotension . 2) Small-volume resuscitation increases CSF osmolality in humans suggesting that stimulation of the central vasomotor center is one of the mechanisms of action.

THE INFLUENCE OF HYPERTONIC-HYPERONCOTIC INFUSION ON THE EXCRETION OF ATRIAL NATRIURETIC FACTOR (ANF) IN NORMOVOLEMIA.

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Background: I. Hypertonic-hyperoncotic solutions (**HHT**) are used in many emergency as well as intensive care studies for resuscitation of patients in any type of shock[1]. II. Due to studies by Gauer, Henry and Reeves[2], later by De Bold and Sonnenberg[3], the human atrial natriuretic factor (**hANF**) is described as potent inductor of diuresis, natriuresis and increase of GFR. Up to now there exist various hypotheses about the physiological mechanisms to be most responsible[3,4,5] for excretion of ANF. III. No studies in patients exist to demonstrate the effects of **HHT** - in relation to sodium-load and volume-expansion - versus **HES** - with only volume-expansion.

Methods: 23 awake patients were enclosed into the study (11 **HHT**-, 12 **HES**-group), directly before aneurysmectomy of the infrarenal abdominal aorta. With permission of the local Ethic Committee of Research we applied either ***hypertonic***-saline (**HHT** - 7.5 % NaCl / 10 % HES 200 / 0.5) or ***isotonic***-saline (**HES** - 0.9 % NaCl / 10 % HES 200 / 0.5) as stepwise infusion of 50 ml preoperatively in randomized, double-blind and controlled manner. Volume-loading was performed according to the individual Frank-Starling-relation until highest cardiac output with lowest possible filling pressure (≡ "best-wedge-condition") was reached. CVP and PCWP were measured by Swan-Ganz-catheterization before, during and after volume-application. ANF and cGMP, second messenger of ANF, were analysed by radioimmunoassay. Arterial blood-tests were taken before, 1, 10, 30 and 60 min after application of each solution. Statistics were performed with t-test, Wilcoxon-test and Mann-Whitney-test for dependent and independent study-groups.

Results: For individual "best-wedge-condition" 213.6 (± 63.6) ml HHT and 409.9 (± 136.2) ml HES were necessary [$p<0.001$]. Due to pharmacological composition of HHT, this group was loaded with 273.9 (± 81.5) mmol sodium and HES-group with 63.1 (± 21.0) mmol sodium [$p<0.001$]. In verum-group PCWP increased to 14.9 (± 4.3) mmHg and CVP to 6.9 (± 2.9) mmHg, in control-group PCWP to 14.5 (± 4.3) mmHg, CVP to 7.5 (± 3.2) mmHg [for all: $p<0.001$]. Plasma-ANF increased in both study-groups in identical manner. Levels of ANF doubled as well after HHT [$p<0.01$] as after HES-infusion [$p<0.05$]. Levels of cGMP increased in both groups in parallel manner, 10.5 (± 4.2) nM [$p<0.01$] resp. to 12.6 (± 5.8) nM [$p<0.001$]. We could not find any statistical difference between the two study-groups.

Conclusion: I. Right and left ventricular expansion described as increase of CVP and PCWP are identical after volume-load with either HHT or HES, but in different dosage. II. Increase of ANF-levels represents same right atrial dilation with different volumes of both infusions (double volume in HES-group). III. Stimulus for ANF excretion is dilation of right atrium by acute volume-expansion. IV. Acute sodium-load has ***no effects*** on ANF-excretion.

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EFFECT OF HYPERTONIC FLUIDS ON ICP & BRAIN WATER CONTENT IN COMBINED HEAD INJURY AND HEMORRHAGIC SHOCK.

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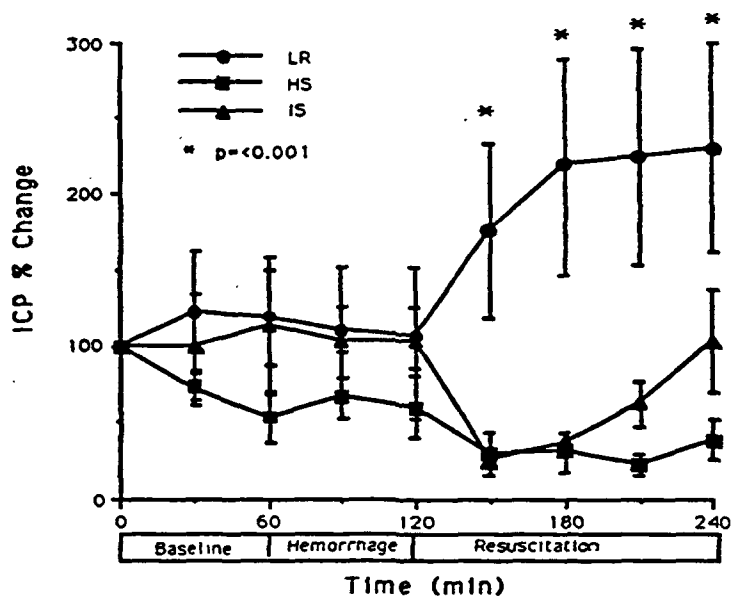
Background: Standard resuscitation protocols for management of hemorrhagic shock may have a deleterious effect on the injured brain. We studied the effects of a new hypertonic fluid Isosal (a 2400 mosm/L hypertonic mixture of saline, glucose and amino acids), and Hypertonic Saline (HS) (7.4%, 2400 mosm/L), compared to Lactated Ringers solution (LR) in a sheep model of severe hemorrhage and associated head injury.

Methods: Adult female sheep were anesthetized and instrumented for hemodynamic measurements. Cryogenic brain injury was created on the right parietal dural surface, and Intracranial pressure (ICP) was monitored from the opposite hemisphere. The animals were bled until the cardiac output (CO) decreased to 50% of its baseline value. Resuscitation was done, initially, with 8 cc/kg bolus of one of the 3 study fluids, followed by LR as needed to return CO to baseline and maintain it for 2 hours.

Results: A total of 13 animals were studied. There was no significant difference in the total fluid requirement for resuscitation between groups. ICP was significantly higher in the LR group ($p=< 0.001$ ANOVA). Brain water content on the injured side was significantly higher in the LR group ($p=0.03$).



Conclusions: Isotonic resuscitation fluid (LR) increases ICP and brain edema when hemorrhagic shock is associated with head injury. Hypertonic fluids(Isosal and HS) are effective as resuscitation fluids and decrease ICP and brain water content.

COMPARISON OF 7.5% NaCl/ 6% DEXTRAN-70 RESUSCITATION OF HEMORRHAGE BETWEEN EUHYDRATED AND DEHYDRATED SHEEP.

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Background: 7.5% NaCl-6% Dextran-70 (HSD) has been shown to be an effective, small volume resuscitation fluid following hemorrhage (HEM) in euhydrated sheep. However, there is controversy whether hypertonic, hyperoncotic solutions would be effective in dehydrated state. This study was designed to address this question.
Methods: We used chronically-instrumented, adult ewes to study the hemodynamic, plasma, and urinary excretion responses to HSD following HEM. One group was studied in the euhydrated state (E), the other was studied after 4 days of dehydration (D). All sheep were bled to 50 mmHg mean arterial pressure (MAP). After 2 h of hypotension, they received a 4 ml/kg bolus of HSD. Data were collected over 90 min.
Results: Data for mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), total peripheral resistance (TPR), stroke volume (SV), plasma Na (P_{Na}) and protein (PTP) concentration, urine flow rate (V), Na (Ex_{Na}), and dextran excretion rate (Ex_{Dex}) at the baseline (BL), 2 hr of HEM (H120), and 90 min after resuscitation (R90) are shown in the table. This increase in PNa was not associated with any observable adverse effects on the sheep.*P<0.5 different from BL. +E different from D.

		BL	H120	R90		BL	H120	R90
MAP	E	94±4	52±1*	81±3	P_{Na}	150±3	150±4	157±4
mmHg	D	86±4	57±3*	81±2	mEq/L	157±2	158±2	166±3
HR	E	87±9	98±15	133±21	PTP	7.8±0.1	6.1±0.4	5±0.2
bpm	D	91±4	150±19	148±7	g/dl	8.9±0.6	7.4±0.5	5.8±0.4
CO	E	5.3±0.4	2.5±0.1*	5.4±0.5	V	0.5±0.1	0.2±0.1	1.0±0.2
L/min	D	4.0±0.3	2.0±0.1*	3.7±0.1+	ml/min	0.3±0.1	.03±.01+	0.5±0.1
TPR	E	18±1	23±2	16±2+	Ex_{Na}	22±8	8±2	173±41
PRU	D	22±1	32±3+	22±2+	µEq/min	6±2	1.5±0.4	58±20
SV	E	60±4	31±3*	49±6*	Ex_{Dex}	0	0	18±1
ml/b	D	44±4+	14±2*	25±1+	mg/min	0	0	13±4

Conclusion: HSD was as effective in resuscitating dehydrated sheep as it was with euhydrated sheep, restoring values back to BL MAP, CO, and TPR, and this was accomplished without excessive V or ENa.

HYPERTONIC SALINE IN THE TREATMENT OF ACUTE LIMB ISCHEMIA

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Background: Acute limb ischemia has been shown to result in acute activation of cascade systems and myocardial depressant effects (1). Hypertonic saline (HS) is considered to enhance capillary blood flow and to improve cardiovascular function. The present study was initiated to assess the value of HS in the treatment of experimental acute distal aortic occlusion.
Methods: A previously described porcine model for acute distal aortic occlusion was used (2). In anesthetized Swedish landrace pigs (n=24) acute distal aortic occlusion was induced. Heart rate, blood pressure, cardiac output, stroke volume, thoracic fluid index, ventricular ejection time, ejection velocity index, peripheral skin blood flow, and blood chemistry were monitored. At the start of the experiment, after 4 hours of incomplete ischemia as well as after 15 and 180 min of reperfusion skeletal muscle biopsies were taken for analysis of high energy phosphagens and lactate. At reperfusion fluid treatment was given as A) Normal saline (NS); B) 7,5% HS; or C) 7,5% HS+Dextran 70 (HSD), 4 ml/kg b.w. during 10 min. The infusion was started 5 min prior to release of occlusion.
Results: Aortic occlusion resulted in increased MAP and HR, while SVI as well as peripheral limb blood flow decreased. At reperfusion MAP, SVI, and SVR decreased, HR increased, and CI remained mainly unchanged. Cardiac contractility was reduced at reperfusion, more so in NS than in HS and HSD groups. The central hemodynamic consequences at the release of the aortic occlusion were attenuated by treatment with the HS-fluids although significant differences between HS and HSD were not demonstrable. The hemodilution seen after HS or HSD was more pronounced than after NS but no significant differences in effects on skeletal muscle high energy phosphagen metabolism were seen. Lactate clearance from skeletal muscle was enhanced by HS.
Conclusion: HS treatment of acute subtotal 4-hour limb ischemia attenuates the myocardial and hemodynamic disturbances seen at reperfusion and enhances skeletal muscle lactate clearance

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Efficacy of Hypertonic Saline/Dextran (HSD) or Hypertonic Saline (HS) on Survival Following Traumatic Injury: A Meta-Analysis

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Previous studies of the efficacy of 2400 mOsm NaCl/Dextran (HSD) or 2400 mOsm NaCl alone (HS) in the treatment of trauma have been inconclusive due to the inability to attain adequate sample sizes. We undertook the present study to review previous studies of HSD and HS and to analyze possible effects in the treatment of trauma. Studies were attained from the published literature and by survey (by letter) of 26 investigators known to be leaders in the field of hypertonic saline and trauma to identify unpublished work. In total, 35 studies using HSD or HS were identified in which 1,400 patients were treated with 2400 mOsm NaCl. Of these, 12 studies used the solutions in the treatment of trauma. Three were excluded as they were reports of interim data. Nine of these met the entry criteria of the present study. In the selected studies, enrollment criteria were consistent: injury resulting in a systolic blood pressure of less than 100 mm Hg. In some of the studies, both HSD and HS were evaluated. Survival for 30 days or discharge was selected as the primary end point and was compared to standard isotonic treatment (LR).

	HS	LR	HSD	LR
Total Treated	340	379	588	582
Survived	235	262	441	407
% Survival	69.1	69.1	75.0	69.9

Meta-analysis was performed by pooling the results from individual studies. The difference in survival rate (DSR) between HS and HSD and respective LR groups was estimated. Pooling was performed by calculating the weighted mean and SE of the DSRs. A Mantel-Haenszel summary odds ratio was obtained from the 8 studies for 24-hr survival in the HS or HSD vs LR groups. Analysis showed the null hypothesis could not be rejected. For HS p=0.94 two tailed test, and for HSD p=0.051. In 7 out of the 8 studies in which HSD was compared with LR, survival rates were higher with HSD. The odds ratio was estimated to be 1.303 in favor of HSD with a 95% confidence interval of .999 to 1.700. We conclude from the meta-analysis that HSD resuscitation for treatment of traumatic hypotension may improve survival compared to standard of care. Further, HS alone is not more efficacious than LR.

RESUSCITATION OF UNCONTROLLED HEMORRHAGIC SHOCK USING HYPERTONIC SOLUTIONS AND LACTATED RINGER'S

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Background: Prehospital resuscitation of hemorrhagic shock consists of aggressive large volume crystalloid therapy. In the presence of an uncontrolled vascular injury this therapy may increase secondary internal hemorrhage. Hypertonic saline dextran (HSD) reduces the volume requirements, but can rapidly increase arterial pressure, which may contribute to secondary hemorrhage. In addition, chloride loads often exacerbate pre-existing acidemia. Hypertonic acetate dextran (HAD) may reduce secondary hemorrhage volumes due to its strong vasodilatory affects while still providing organ perfusion. Acetate substitution also provides isochloremic resuscitation thus reducing hyperchloremic effects. We compared the effectiveness of resuscitation with lactated Ringer's (LRS), HSD and HAD in an uncontrolled hemorrhage model infused with a "limited prehospital resuscitation" (LPR) regimen designed to partially restore cardiovascular function.

Methods: Three groups of Yorkshire swine (n=8) were instrumented with arterial, venous and pulmonary catheters. Following a splenectomy, an aortotomy wire was implanted in the ventral abdominal aorta. Animals were ventilated to normocapnea and set at fixed minute volumes. Baseline hemodynamics were monitored for 30 min., followed by 30 min. of controlled hemorrhage in which 25 ml/kg (35%) blood was removed. The aortotomy wire was pulled, creating a 5mm laceration in the aorta and uncontrolled intra-abdominal hemorrhage. The animals were left undisturbed for 20 min. and then treated with LRS, HSD or HAD infused from coded bags blinded to the investigators. Fluids were administered using an LPR regimen until 60% baseline cardiac output (CO) was achieved, or a maximum of 10 ml/kg was infused. After 20 min., the aortotomy was surgically repaired, and resuscitation continued using LRS as needed to maintain 80% baseline mean arterial pressure (MAP) for 120 min. to simulate an intraoperative resuscitation (IOR) regimen.

Results: Both HSD and HAD significantly reduced fluid requirements during LPR, while only HAD reduced intraoperative volume requirements (Table). 10 ml/kg was not sufficient to achieve and maintain 60% baseline CO in 5 of 8 LR animals. However, 60% CO was achieved in all HSD and HAD animals with less than 10 ml/kg. CO was significantly higher during LPR in the HAD group compared to LRS and HSD. No difference was seen during IOR. MAP remained low during LPR (36-45 mmHg) in all groups, but were increased from hemorrhage levels (19-27 mmHg) although CO was elevated. Secondary hemorrhage volumes (peritoneal fluid) did not significantly differ between the groups, but HAD animals lost significantly less hemoglobin (Table). Base excess (BE) significantly increased in the HAD during LPR (Δ+1.6 mmol/dl) compared to HSD (Δ-3.5 mmol/dl) and LRS (Δ-2.0 mmol/dl). HSD BE did not begin to recover until 60 min. of IOR. LRS BE did not increase from hemorrhage during IOR. Changes in pH and HCO_3^- corresponded with those of BE.

group	prehospital fluids in (ml/kg)	intraoperative fluids in (ml/kg)	peritoneal fluids lost (ml/kg)	hemoglobin lost (g/kg)
LRS	9.4 ± 0.6	111.8 ± 15.6	7.2 ± 1.3	0.22 ± 0.07
HSD	4.5 ± 1.1*	106.9 ± 29.5	11.2 ± 4.8	0.31 ± 0.12
HAD	2.4 ± 0.4*	55.3 ± 11.3*	6.4 ± 1.4	0.08 ± 0.02*

Conclusions: Combinations of hypertonic solutions and a "limited prehospital resuscitation" regimen may effectively treat severe hemorrhagic shock without effecting secondary blood loss. HAD may provide superior acid-base balance and cardiovascular efficiency compared to HSD or LRS for the prehospital treatment of trauma.

EFFECTS OF NACL 7,2% / 10% DEXTRAN-60 ON GLOBAL AND LOCAL MYOCARDIAL PERFORMANCE DURING RESUSCITATION FROM HEMORRHAGIC SHOCK

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Background: In isolated muscle hypertonic saline increases contractility in an osmolarity dependent manner. Dextran is a radical scavenger and inhibits post-reperfusion leucocyte sticking and thus may improve myocardial performance after resuscitation. However, the effects of small volume resuscitation (SVR) using a combination of hypertonic NaCl (7,2%) and hyperoncotic dextran (10%; HSHDex) on myocardial performance have not been investigated in the intact organism. Therefore, we assessed during resuscitation from hemorrhagic shock in pigs endsystolic elastance (Ees) as well as segmental and global preload recruitable stroke work (sPRSW, PRSW), relatively load independent parameters of myocardial contractilityity.
Methods: In 12 pentobarbital/piritramid anesthetized ventilated pigs (28±4 kg) hemorrhagic shock was induced by withdrawl of blood to decrease mean arterial pressure (MAP) to 45 mmHg for 75 min. Central hemodynamics, left ventricular volume (LVV, conductance technique), left ventricular pressure (LVP, tip manometer), and myocardial segment length (ultrasonic crystals) were measured at 'Control', end of shock ('Shock'), 5 min ('5 pR'), and 60 min ('60 pR') after infusion of either HSHDex (10% of shed blood volume, n=6) or the identical osmotic load of isotonic NaCl (n=6). At '30 pR' isooncotic 6% dextran-60 (10% of shed blood volume) was given in both groups. LVP-volume and LVP segment-length relations were obtained under varying loading conditions induced by rapid caval occlusion. Left ventricular dP/dt, segmental shortening (SS), maximal velocity of segment shortening at zero load (Vmax), sPRSW, PRSW, and Ees were assessed. For statistics ANOVA, rANOVA and Wilcoxon-test were used.Data are presented as mean ± SD.
Results: Shock decreased dP/dt ($p<0.05$) and SS (HSHDex -68%, $p<0.01$; NaCl -50%, $p<0.05$) while Vmax increased (HSHDex +36%, $p<0.01$; NaCl +29%, $p<0.05$). Shock did not alter PRSW and sPRSW significantly. Negative Ees was observed in 3 of 6 animals in both groups at 'shock'. HSHDex increased osmolarity from 310±6 to 327±9 mosmol/l at 5 pR. Both, HSHDex and NaCl normalised CI and increased MAP at 5 pR, while at 60 pR MAP was higher with HSHDex (HSHDex 89±17 *vs.* NaCl 67±7 mmHg, $p<0.05$). At 5 pR dP/dt rose with either therapy (HSHDex +34%, $p<0.01$; NaCl +37%, $p<0.05$) while Vmax, PRSW and sPRSW remained unchanged. SS significantly improved with HSHDex (HSHDex +58%, $p<0.01$, NaCl +20%, n.s.). After resuscitation negative Ees was neither observed with NaCl nor with HSHDex. Local and global preload, measured as segment length and LVP at enddiastole, increased at 5 pR in both groups, but were higher at 60 pR with HSHDex ($p<0.05$).
Conclusion: Immediate hemodynamic stabilisation after resuscitation with HSHDex can not be attributed to increased myocardial contractility. Hemodynamic stabilisation is prolonged after SVR with HSHDex as compared to resuscitation using an eight times larger volume of NaCl primarily due to increased left ventricular preload.

PROGNOSIS FOLLOWING THE ADMNISTRATION OF HYPERTONIC/HYPERONCOTIC SOLUTIONS IN HYPOVOLEMIC PATIENTS.

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Background: Previously published trials on hypertonic solutions show effective improvements in hemodynamic parameters of patients admitted to the Emergency Room, but no significant differences in outcome compared to standard isotonic treatment.

Methods: This study evaluates pretreatment prognostic factors that predict a beneficial effect of hypertonic solution in patients admitted to the Emergency Room with hemorrhagic hypovolemia in a prospective double-blind fashion. The patients (n=212) were randomized upon admission to receive 250 ml IV bolus of hypertonic 7.5% NaCl + 6% dextran 70 (HSD, n= 101), or isotonic 0.9% NaCl solutions (IS, n= 111) followed by standard resuscitation. Pretreatment factors assessed were: Sex, age, cause of hypovolemia, Revised Trauma Score (RTS), Glasgow Index, and mean arterial pressure (MAP).

Results: HSD administration significantly increased MAP, and reduced IV crystalloid infusions. There were no differences in blood transfusions. Overall complication rates were similar in both groups (24%). Overall survival rate was a significantly lower ($p<0.03$) in IS, vs HSD groups. Twenty-four hours survival rate was also significantly lower ($p=0.007$) in IS (72%), compared with HSD (87%). Multivariate analyses identified RTS and MAP as independent predictors for 24 hour survival in the group that received HSD. When evaluated for overall survival rate, HSD infusion benefited significantly only patients with MAP < 70 mm Hg ($p<0.01$).

Conclusions: This is the first study to show a significant difference in survival between HSD and conventional treatment for hemorrhagic shock.

7.5% NaCl / 4.2% HETASTARCH DECREASES POSTOPERATIVE EDEMA, ICU DAYS, AND TIME TO DISCHARGE IN ORTHOGNATHIC SURGERY PATIENTS.

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BACKGROUND: Numerous studies have demonstrated the clinical effectiveness of hyperosmotic/hyperoncotic solutions in resuscitating hypovolemia secondary to a variety of causes. Prospective trials using 7.5% NaCl/Dextran 70 in trauma patients have shown increased survivability following low volume fluid resuscitation compared to resuscitation with Ringer's lactate. Other studies have demonstrated an attenuated hormonal response to injury; decreased third spacing post operatively; and improved resuscitation in burn patients. Hyperosmotic solutions have also been shown to decrease ICP while maintaining intravascular volume. The purpose of our study was to evaluate the effect of 7.5% NaCl/4.2% Hetastarch on postoperative facial edema, ICU requirements and time to discharge in patients undergoing radical orthognathic surgery.
METHODS: Thirty-five consecutive orthognathic surgery patients were studied prospectively and compared retrospectively to the 62 previously consecutive patients. Demographics of the two groups were not significantly different, nor were the types or complexities of procedures. The prospective group received a protocol anesthetic: preoperative midazolam 3 mg IV; and induction with sufentanil 0.5 mcg-kg^{-1}, vecuronium 0.1 mg-kg^{-1}, and thiopental titrated to sleep; maintenance with sufentanil 0.25 to 0.5 mcg-kg^{-1}-hr^{-1} and isoflurane to maintain mean arterial blood pressure between 58 and 62 mmHg. Ketorolac 60 mg IM and dexamethasone 0.4 mg-kg^{-1} IV were administered prior to incision. Baseline laboratory studies consisting of serum sodium and osmolality and urine sodium, osmolality and specific gravity were obtained after an intraarterial catheter was established. 7.5% NaCl/4.2% hetastarch (5 ml-kg^{-1}) was then administered over 30 minutes through a peripheral IV. Thirty minutes following hypertonic saline (HS) infusion, serum sodium and osmolality were determined, and three hours post HS infusion, urine sodium, osmolality and specific gravity were measured. Facial edema was subjectively scored by the same surgeons in both groups on a scale from 0 to 3^{+}.
RESULTS: In the prospective group, pre HS serum sodium ranged from 134-146 m mol-L^{-1} ($\bar{x}$ = 139 +/- 3.0 SD). Serum osmolality ranged from 275-298 mosmol-kg^{-1} ($\bar{x}$ = 286 +/- 6.9). Following HS administration, serum sodium ranged 147-160 ($\bar{x}$ = 152 +/- 3.2) and serum osmolality ranged 305-329 ($\bar{x}$ = 314 +/- 8.7). Estimated blood loss between groups was not significantly different. Significant between group differences were found in total crystalloid administered ($\bar{x}$ = 3.44 L retro group vs. 1.20 L pro) and in urine output ($\bar{x}$ = 2.04 ml-kg^{-1}-hr^{-1} retro vs. 0.49 pro). Significant between group differences were also found in the study variables: (1) 74% of retro patients developed 2^{+} or 3^{+} facial edema while 68% of the pro group developed 0 or 1^{+} edema. (2) No prospective patients were admitted to the ICU, while 44% of the retro group remained in the ICU 1 to 3 days. (3) Hospital stay was reduced prospectively to $\bar{x}$ = 1.6 days from $\bar{x}$ = 2.5 days.
CONCLUSIONS: The study can be criticized for a retrospective control and lack of quantification of facial edema. However, the results demonstrate the usefulness of systematically incorporating hypertonic saline into an anesthetic protocol to solve a morbidity problem in a well defined patient population. Patients emerged smoothly from anesthesia, and all were extubated promptly in the operating room or the PACU with minimal edema and without discomfort. Development of the protocol has produced a marked decrease in overall cost to our patients, many of which pay out-of-pocket for these procedures. Patient follow-up to one year in the oral surgery clinic has produced no complaints of gross neurological or renal changes.

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